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Editorial Open Access

Journal of Surgery at its 10th Anniversary

R Moldovanu[1,2*] **and E Târcoveanu**[2]

[1]*Department of Surgery and Oncology, Les Bonnettes Hospital, Arras, France*

[2]*Department of Surgery, University of Medicine and Pharmacy, "Gr. T. Popa" Iaşi, Romania*

[*]**Corresponding author**: Radu Moldovanu, MD, PhD, Department of Surgery and Oncology, Les Bonnettes, Hospital, Arras, France, 2 rue Dr. Forgeois, 62012, Arras, France, Tel: +33 (0) 321154388; Fax: +33 (0) 321602258; E-mail: rmoldovanu@gmail.com

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Abstract

Journal of Surgery [Jurnalul de chirurgie] is now at its 10th anniversary. It was developed after the success of the first Romanian medical e-teaching/e-learning platform, www.laparosurg.ro. The mains goals of the new journal were to ensure a powerful platform for medical information/education and to allow to the residents and young doctors to publish and share their research work. Even from its first volume Journal of Surgery was included in DOAJ (Directory of Open Access Journals) a worldwide data base developed by Lund University from Sweden. Then, the journal was included in other prestigious international databases as Index Copernicus and EBSCO Academic. During the last 9th volumes, Journal of Surgery published 547 scientific articles that means 60.77 ± 13.07 articles yearly (median 55; range 44 to 86) distributed in 4175 pages (463.89 ± 117.23 pages/year, median 421, range: 372 to 721). The overall tendency was to slightly increase the number of articles. It is important to note the stability of published editorials, multimedia, case reports, surgical technique notes and history of surgery articles; furthermore due to the tightening of the peer review process we noted a bipolar tendency regarding original papers and review type articles: to increase the number of original paper and, respectively, to decrease the number of reviews. In this way the review type articles decreased from over ten articles per year (the first 4 issues) to 5 and respectively, 7 in the last two years, and the original articles increased from about 12/year in the first 4 years to over 20 in the last three years. The citation of Journal of Surgery's articles is also on an increasing tendency. A brief electronic data research revealed 142 citations (from 386 articles studied). The other overall scientific data measurements are: 0.37 cites/paper, 15.78 cites/year an h-index of 5 and a g-index of 9. In this era of globalization, of open access, of "impact factor", of performance and "performance" classifications, the surgical journals are "under pressure". The only way to evolve, to improve the scientific content and to be "more international" is to open all the barriers and misconceptions. In this way, Journal of Surgery has joined to OMICS group. This new collaboration allows us to further develop the Journal (with a primary objective to be included in PubMed and then in ISI) and to widely open the Romanian surgery to the world. Furthermore we want to offer to the young doctors a powerful surgical education platform and a real chance to share their work to their colleagues from all-around the world.

However, our goal to represent Romanian surgery is not forgotten; so, Journal of Surgery will preserve a Romanian language section for the articles submitted in Romanian. We want to warmly thank to all our readers, editors, members of scientific committee and especially to our contributors who helped us during the years to develop Journal of Surgery. We'll remain your true fellows and we invite you to further collaborate with Journal of Surgery.

Keywords: Journal of surgery; Scientific Data; Scientific metrics

Editorial

Journal of Surgery [Jurnalul de chirurgie] is now at the 10th volume; ten volumes and respectively ten years of unbreakable and continuous publication without missing or multiple issues.

Journal of Surgery was developed after the success of the first Romanian medical e-teaching/e-learning platform, www.laparosurg.ro, edited by First Unit of Surgery, Department of Surgery, University of Medicine and Pharmacy "Gr. T. Popa" Iasi, Romania [1]. The mains goals of the new project were to ensure a powerful platform for medical information/education and to allow to the residents and young doctors to publish and share their research work. In this way, Journal of Surgery was designed as an online surgical magazine which was publishing the "classical" types of articles (editorials, reviews and up-to-date articles, original papers and case reports) but also new types as surgical technique notes (how to do it …) and surgical anatomy papers, as well as multimedia articles (power point presentation of lectures or videos). To highlight the Romanian surgical tradition, a *history of surgery* section was also created. Now, this section includes two types of articles, the "standard type" with articles from history of surgery and "Arch beyond time" section developed by Prof. N.M. Constantinescu, which continues the similar section from Romanian surgical magazine *Chirurgia [Surgery]* which re edits and comments older articles published in *Chirurgia [Surgery]* during the dawn of 20th century. To allow a wide opening to the young doctors, *Journal of Surgery* was sharing the open access concept described even from the dawn of the Modern Era by Ralph Waldo Emerson: "*knowledge exists to be imparted*" [2]. So, even from its first volume *Journal of Surgery* was included in DOAJ (Directory of Open Access Journals) a worldwide data base developed by Lund University from Sweden [3]. Then, the journal was included in other prestigious international databases as Index Copernicus and EBSCO Academic. A

plan to include *Journal of Surgery* in PubMed is in course; in this way a first evaluation in 2012 noted a score of 3.5 from 5 in term of scientific and technical issues.

From then a new protocol to improve data transfer (metadata format, XML format) was implemented and a new academic interface for *.pdf documents (two columns, academic presentation for tables and pictures) was designed. From two years, *Journal of Surgery* was included in CrossRef® and a DOI (Digital Object Identifier) was attributed: 10.7438/1584-9341. In this way the interrelations with different databases and citations reports were improved.

From the beginning *Journal of Surgery* was published under the appointment of the First Surgical Unit, Department of Surgery of "Gr. T. Popa" University of Medicine and Pharmacy Iași, Romania and with the constant help of "St. Spiridon" Trustee Iași; then, *Journal of Surgery* was recognized as an important tool in medical education and research dissemination, and in present days, is affiliated to *Romanian Society of Surgery* and *Academy of Medical Sciences Iași.*

The increasing of the scientific level of the published articles was a constant concern; in this way systematic peer review process was developed. The needs of young doctors to share their work and to find in the journal's pages a real tool for their surgical education led us to keep and develop the "case report" and "surgical technique" sections. In our opinion, despite the actual tendency of the scientific journals to give up to this type of articles, these articles are really necessary for medical education; in fact this policy reflects the thoughts of philosophers: *"you teach what you have to learn" [4] and respectively,* "*the art of teaching is the art of assisting discovery"* [5].

So, during the last 9th volumes, Journal of Surgery published 547 scientific articles … that means 60.77 ± 13.07 articles yearly (median 55; range 44 to 86) distributed in 4175 pages … (463.89 ± 117.23 pages/year, median 421, range: 372 to 721). The overall tendency was to slightly increase the number of articles. It is important to note the stability of published editorials, multimedia, case reports, surgical technique notes and history of surgery articles (Figure 1); furthermore due to the tightening of the peer review process we noted a bipolar tendency regarding original papers and review type articles: to increase the number of original paper and, respectively, to decrease the number of reviews.

In this way the review type articles decreased from over ten articles per year

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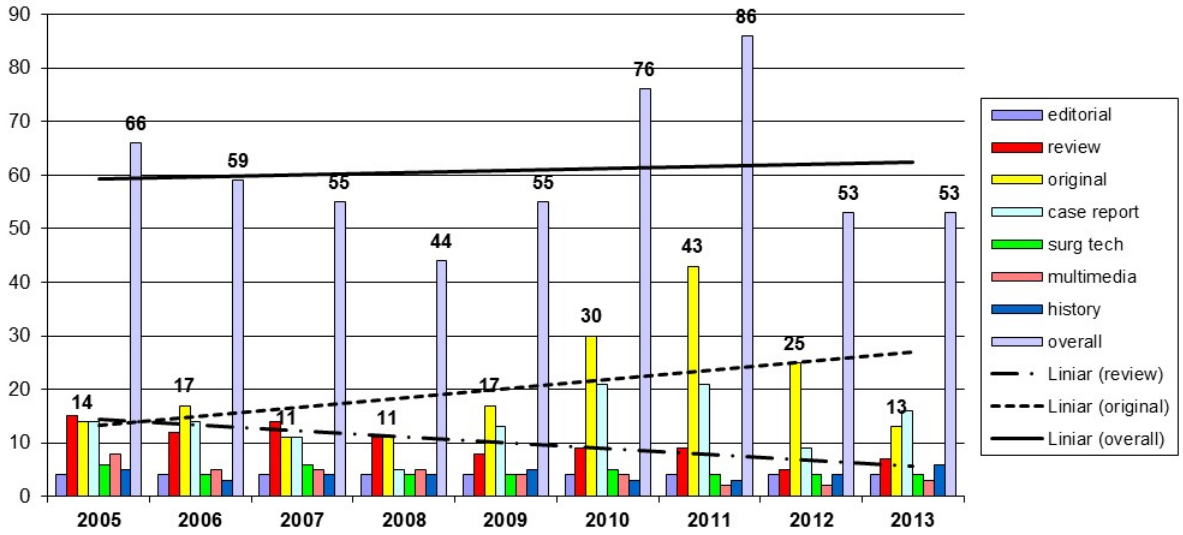

Figure 1: Distribution of published articles from 2005 until nowadays. To note the tendencies lines from original and review type articles.

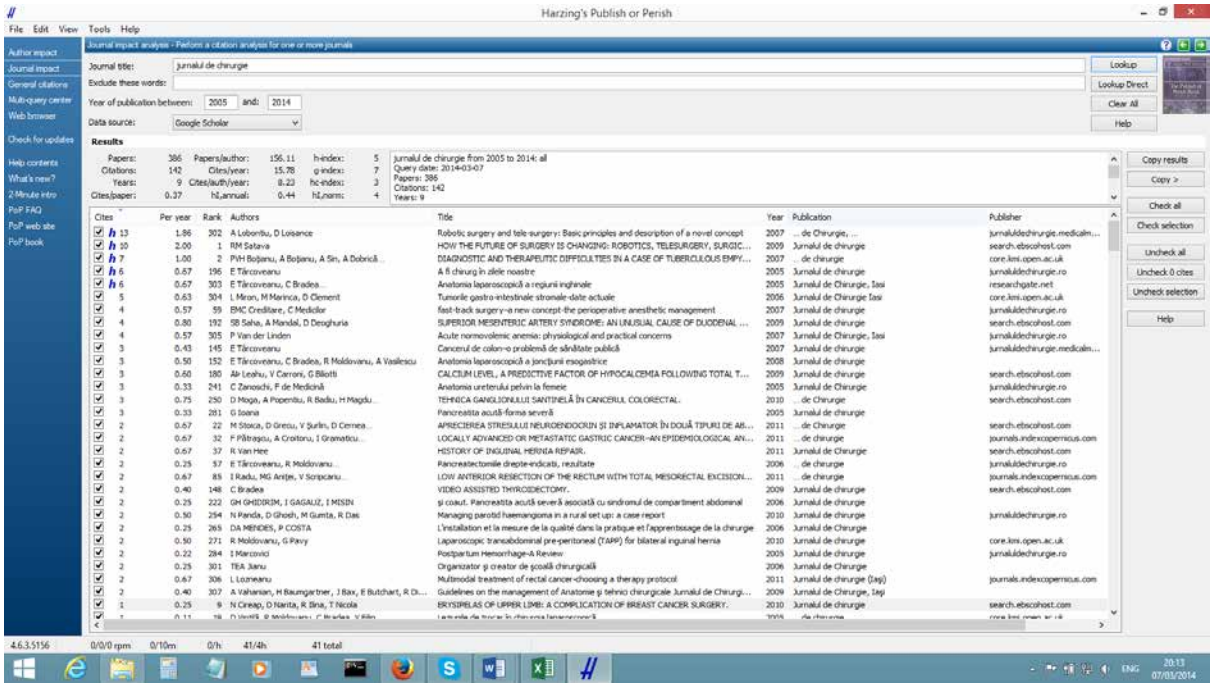

Figure 2: Scientific *Journal of Surgery's* metrics using *Harzing's Publish or Perish software* [6].

The citation of Journal of Surgery's articles is also on an increasing tendency. A brief electronic data research using *Harzing's Publish or Perish* [6] software, revealed 142 citations (from 386 articles studied). The first three cited articles are:

Lobontiu A, Loisance D. ROBOTIC SURGERY AND TELE-SURGERY: BASIC PRINCIPLES AND DESCRIPTION OF A NOVEL CONCEPT. *Jurnalul de chirurgie* (Iasi) 2007; 3(3): 208-214, with 13 citations (1.86 citations/year);

Satava RM. HOW THE FUTURE OF SURGERY IS CHANGING: ROBOTICS, TELESURGERY, SURGICAL SIMULATORS AND OTHER ADVANCED TECHNOLOGIES. *Jurnalul de chirurgie* (Iasi) 2009; 5(4): 311-325, with 10 citations (2 citations/year);

Botianu PHV, Botianu A, Sin A et al. DIAGNOSTIC AND THERAPEUTIC DIFFICULTIES IN A CASE OF TUBERCULOUS EMPYEMA WITH ATYPICAL MYCOBACTERIA. *Jurnalul de chirurgie* (Iasi) 2007; 3(1): 45-51, with 7 citations (1 citation/year).

It is important to note that several articles are cited by international prestigious journals like:

World Journal of Surgery (Satava RM. HOW THE FUTURE OF SURGERY IS CHANGING: ROBOTICS, TELESURGERY, SURGICAL SIMULATORS AND OTHER ADVANCED TECHNOLOGIES. *Jurnalul de chirurgie* (Iasi) 2009; 5(4): 311-325),

Surgical endoscopy (Lobontiu A, Loisance D. ROBOTIC SURGERY AND TELE-SURGERY: BASIC PRINCIPLES AND DESCRIPTION OF A NOVEL CONCEPT. *Jurnalul de chirurgie* (Iasi) 2007; 3(3): 208-214 and Vintilă D, Moldovanu R, Vlad N et al. TROCARS INJURIES IN LAPAROSCOPIC SURGERY. *Jurnalul de chirurgie* (Iasi) 2005; (1)1: 53-56),

American Journal of Medicine (Cotea E, Vasilescu A, Dimofte G et al. GASTRIC DIVERTICULA ON THE GREATER CURVATURE. *Jurnalul de chirurgie* (Iași) 2007; 3(3): 269-273) etc.

The other overall scientific data measurements are: 0.37 cites/paper, 15.78 cites/year an h-index of 5 and a g-index of 9 (Figure 2).

In this era of globalization, of open access, of "impact factor", of performance and "performance" classifications, the surgical journals are "under pressure". The only way to evolve, to improve the scientific content and to be "more international" is to open all the barriers and misconceptions.

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Review Article Open Access

Modalități Diverse de Tratament în Cancerul de Col Uterin Clinic Evident (Stadiile I B și II A)

I Păun[1*], D Mogoş[1], Mariana Păun[2], D Ilie[1], M Florescu[1], M Ionescu[3], M Teodorescu[1], CDVidrighin[1], M Racareanu[1], G Mogoş[1] and T Tenea[1]

[1]*Clinica de Chirurgie IV, Spitalul Clinic Căi Ferate, Craiova, Romania*

[2]*Clinica Obstretică Ginecologie, Spitalul Clinic Județean Craiova, Romania*

[3]*Clinica Oncologie, Spitalul Filantropia Craiova, Romania*

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[*]**Corresponding author**: Ion Păun MD, PhD, Assoc. Professor of Surgery, 4th Surgical Unit, Railway University Hospital, Craiova, Str. Știrbei Vodă, No. 6, Romania, Tel: +40 (0) 0723 34 75 72; Fax: +40 (0) 0251 53 24 04; E-mail: dripaun@gmail.com

Abstract

This paper aims to update certain aspects of the therapeutic attitude on cervical cancer, a disease that currently is, worldwide, the second leading cause of cancer death in women and thus has increasingly come to the attention of general surgeons. The obvious clinical forms of cervical cancer are brought into discussion, meaning those in the FIGO IB1, IB2 and IIA stages, these being, by far, the most numerous cases we meet in the clinic. Unlike early cervical neoplastic lesions (stages 0 and IA) where the therapeutic attitude is relatively well codified and uniform, in obvious clinical forms there is a great variability of therapeutic approaches, with results that are close to those from the studied literature, indicating according to various statistics a survival rate at 5 years of 80% and 90% for stage I disease and between 60% and 80% for stage II patients.

Keywords: Cervical Uterin Cancer; Radical Hysterectomy; Radiotherapy; Chemotherapy

Introducere

Cancerul de col uterin continuă să reprezinte o problemă de sănătate, peste tot în lume fiind a doua mare cauza de deces prin cancer în rândul femeilor cu peste 500.000 de cazuri noi diagnosticate anual și cu o rată a mortalității de aproximativ 50% [1]. Dintre cazurile noi diagnosticate, aproximativ 79% apar în țările în curs de dezvoltare în timp ce în Statele Unite, cancerul de col uterin este a șasea leziune malignă, ca frecvență, în rândul femeilor cu 12.900 noi cazuri diagnosticate pe an și cu aproximativ 4.400 decese anual [1].

Aceste discrepanțe se explică prin diferențele privind implementarea programelor de prevenție a cancerului de col uterin, mult mai ferme în țările dezvoltate.

În aceste țări, citologia cervicală reprezintă un foarte bun instrument de screening pentru leziunile pre-invazive, pe când în țările în curs de dezvoltare cele mai multe femei sunt diagnosticate cu forme invazive cu simptomatologie asociată și, în consecință, cu un prognostic mai rezervat [2].

Tratamentul cancerului de col uterin clinic evident

Spre deosebire de leziunile cervicale incipiente (stadiile 0 și IA) unde atitudinea terapeutică este relativ bine codificată și unitară, în formele clinic evidente (stadiile IB și IIA) există o mare variabilitate de abordare terapeutică, cu rezultate foarte apropiate așa cum reiese și din studiile analizate.

Atât chirurgia cât și radioterapia pot fi utilizate ca primă modalitate terapeutică a cancerului de col uterin în stadiile IA și IIA, cu rezultate aparent asemănătoare.

Astfel, Landoni și colab. au analizat, într-un studiu randomizat, rezultatele chirurgiei radicale versus radioterapie în stadiile IB și IIA ale cancerului cervical, negăsind diferențe semnificative nici în ceea ce privește intervalul liber de boală și nici în ceea ce privește supraviețuirea la distanță. Totuși, la 84% dintre pacientele cu tumori cervicale mari (> 4 cm), supuse intervenției chirurgicale radicale ca prim timp, li s-a efectuat radioterapie adjuvantă în condițiile existenței unor factori de risc adiționali [3]. Este recunoscut faptul că, în cazul tumorilor limitate la nivelul colului uterin (stadiul IB), mărimea tumorii constituie un factor predictiv în ceea ce privește supraviețuirea [4].

În acest context apare drept firească subdivizarea în 1994 de către International Federation of Gynecology and Obstretics (FIGO) a stadiului IB în doua sub stadii: IB1 și IB2 stabilindu-se astfel criteriile care diferențiază tratamentul tumorilor mici de cel al tumorilor mari (>4 cm) localizate la nivelul cervixului.

Într-un studiu retrospectiv, publicat în 1996, Finan și colab. raportează faptul că, în urma histerectomiei radicale la pacientele aflate în stadiul IB2 de boală s-a constatat o incidență semnificativ mai mare a metastazelor ganglionare față de cele aflate în stadiul IB1 (44% vs 21%) precum și o rată mai scăzută de supraviețuire la 5 ani (73% vs 90%), în ciuda utilizării mult mai frecvente a radioterapiei postoperatorii la pacientele cu tumori mai mari (72% vs 38%) [5]. Trattner și colab. într-un studiu asemănător, din 2001, constată o supraviețuire postoperatorie la 5 ani de 90% pentru pacientele aflate în stadiul IB1 comparativ cu stadiul IB2 unde supraviețuirea este de numai 40% [6].

În acest context, stabilirea unei terapii ideale pentru cancerul de col uterin aflat în stadiul IB1 ca și în cel aflat în stadiul IIA rămâne controversată datorită în special, numărului limitat de studii randomizate efectuate în acest sens.

Astfel, datele din literatură converg către trei direcții principale de tratament al cancerului cervical aflat în stadiile IB și IIA și anume:

- Histerectomie radicală urmată de radio și eventual chimioterapie;
- Radioterapie și eventual chimioterapie urmată de histerectomie radicală efectuată selectiv sau de rutină;
- Chimioterapie neoadjuvantă urmată de chirurgie, cu sau fără radioterapie postoperatorie.

Histerectomia radicală urmată de radio- și eventual chimioterapie

Efectuarea histerectomiei radicale este cel mai adesea posibilă la pacientele cu cancer cervical aflate în stadiile IB1, IB2 și IIA. În urma intervenției, descoperirea unor factori de risc înalt precum metastazele limfoganglionare, variind între 20% și 50% după diverși autori sau invazia microscopică a parametrelor, care variază între 15% și 29%, determină recomandarea radioterapiei. Din păcate, în aceste situații, la riscurile intervenției chirurgicale radicale se adaugă riscurile posibil generate de terapia radiantă, în special complicații intestinale precum obstrucția sau fistulizarea [7,8].

Incidența recurgerii la radioterapie postoperatorie variază după diverși autori. Astfel, Rettenmaier și colab. recurg la radioterapie în urma intervenției chirurgicale radicale în 35% din cazuri, Bloss și colab. în 50% din cazuri, iar Landoni și colab. folosesc terapia radiantă postoperatorie la 84% dintre pacientele aflate în stadiul IB2 de boală [3,9,10].

Pe de altă parte, toate aceste studii subliniază faptul că prezența factorilor de risc crescut, în urma histerectomiei radicale, este asociată cu scăderea ratei de supraviețuire la distanță.

Ținând cont de toate acestea, o serie de autori au propus asocierea la radioterapia efectuată în postoperator și a chimioterapiei concomitente [11,12].

Astfel, Peters și colab. prezintă datele unui studiu prospectiv randomizat efectuat de două grupuri, Southwestern Oncology Group (SWOG) și Gynecologic Oncology Group (GOG), care au analizat două loturi de paciente prezentând factori de risc crescut după histerectomie radicală si anume: ganglioni limfatici invadați, invazia parametrelor sau margini de exereză pozitive. Un prim lot a fost suspus numai radioterapiei postoperatorii, iar celui de-al doilea lot i s-au efectuat radioterapie si chimioterapie concomitentă presupunând administrarea in bolus de cisplatin și 5-fluorouracil. La lotul suspus chimioterapiei s-a constatat o creștere a procentului de supraviețuire la 4 ani față de lotul suspus numai radioterapiei (80% vs 63%) [12].

În cursul ultimilor 15 ani, Gynecologic Oncology Group (GOG) a identificat, după histerectomia radicală, pe lângă factorii de risc crescut, care agravează prognosticul și o serie de factori de risc intermediari pentru producerea de recurențe precum: volumul crescut al tumorii, profunzimea invaziei miometriale și invazia spațiului limfovascular.

După identificarea acestor factori de risc intermediari pentru producerea recurențelor, GOG a efectuat un studiu randomizat privind intervalul liber de recidive la pacientele la care s-a efectuat radioterapie postoperatorie si la pacientele la care nu s-a mai efectuat niciun fel de terapie după actul chirurgical.

S-a constatat că la 2 ani, absența recidivelor a fost semnificativ mai mare la lotul suspus radioterapiei postoperatorii (88% vs 79%) [13].

Se poate deci afirma că în cazurile în care se constată existența factorilor de risc crescut sau a factorilor de risc intermediari după intervenția chirurgicală radicală pentru neoplasmul cervical se impune efectuarea radioterapiei și eventual a chimioterapiei ca tratament adjuvant.

Avantajele chirurgiei radicale ca prim tratament

Există o serie de avantaje ale terapiei chirurgicale primare față de radioterapia primară în cancerele cervicale în stadiile IB și II A.

Un prim avantaj se referă la evaluarea cu o mai mare acuratețe a extensiei bolii cu identificarea factorilor de risc crescut sau a celor intermediari care reclamă radio- sau chimioterapia postoperatorie.

În plus, examenul histopatologic al piesei de exereză permite aprecierea prognosticului precum și identificarea pacienților prezentând risc crescut de persistență sau de recidivă a bolii [14].

La pacientele aflate în premenopauză și care sunt supuse radio- sau chimioterapiei ca prim tratament al cancerului cervical invaziv, se produce, inevitabil, pierderea funcției ovariene cu consecințele corespunzătoare. În schimb, recurgerea la intervenția chirurgicală ca terapie primară, la această categorie de paciente permite conservarea funcției ovarelor normale.

Sutton și colab. analizând incidența metastazelor ovariene la 991 paciente cu carcinom de col uterin aflat în stadiul IB tratate prin histerectomie radicală și limfadenectomie pelvină într-un studiu prospectiv (1992), au constatat prezența acestor metastaze la 0,5% dintre pacientele cu carcinom squamos și la 1,7% dintre pacientele cu adenocarcinom. La toate aceste paciente au existat pe lângă metastazele ovariene și alte diseminări extracervicale [15]. Studiile efectuate de diverși autori printre care Seibel și colab. de la Universitatea Emory privind efectele tratamentului chirurgical și ale radioterapiei asupra funcției sexuale au relevat faptul că la pacientele supuse radioterapiei se constată o scădere a frecvenței actului sexual, scăderea libidoului și a abilității de a realiza orgasmul [16]. Acest lucru s-ar explica prin modificări marcate ale vaginului sau a țesuturilor paravaginale în urma terapiei radiante. Vaginul se scurtează și are tendința la stenozare, țesuturile din jur devin ferme și fixe, iar mucoasa vaginală este subțire, uscată și are tendința de a sângera. Unele dintre aceste modificări sunt mai pronunțate la femeile tinere în urma hipoestrogenismului indus de menopauza precoce pos-tiradiere. Deși vaginul se scurtează și în urma tratamentului chirurgical, modificările funcționale sunt mult mai puțin evidente.

Din păcate însă, la pacientele supuse radioterapiei postoperatorii se ajunge la aceleași neajunsuri. Pe de altă parte s-a constatat că recurențele si complicațiile in urma tratamentului chirurgical de primă intenție sunt mult mai rare decât cele găsite după radioterapie. Deoarece radioterapia favorizează producerea unei endarterite obliterante progresive, ischemia consecutivă poate favoriza apariția unei complicații tardive precum: cistite, rectite, enterite, pielonefrite, colpocleizis etc.

De aceste elemente trebuie ținut cont atunci când se stabilește indicația tratamentului de primă intenție, în special la pacientele tinere.

Comparativ cu radioterapia primară, tratamentul chirurgical aduce un important beneficiu psihologic la multe dintre paciente, ele simțindu-se încurajate atunci când chirurgul le spune că „tumora a fost îndepartată și că nu există nicio dovadă macroscopică a existenței metastazelor ". În ultimul timp , terapia chirurgicală exclusivă are tot

mai mulți adepți, aceasta atitudine fiind recomandată cazurilor fără invazie ganglionară [17]. În aceste situații se recurge fie la intervenția clasică – colpohisterectomie lărgită – Wertheim - Meigs fie, din ce în ce mai des, în prezent, ca urmare a progreselor chirurgiei celioscopice, la histerectomia radicală pe cale vaginală (procedeul Schauta) precedată de limfadenectomie pelvină laparoscopică [18].

Justificarea limfadenectomiei pelvine

Considerăm că limfadenectomia pelvină ne ajută la realizarea unei disecții adecvate, în jurul tumorii cervicale, ceea ce reprezintă un timp extrem de important în cursul intervenției chirurgicale. Acest lucru se referă în special la acea parte a limfadenectomiei, care implică îndepărtarea țesutului din jurul vaselor hipogastrice, din fosa obturatorie și din porțiunea inferioară a regiunii presacrate.

În ceea ce privește disecția și extirparea ganglionilor para-aortici considerăm că aceasta nu trebuie să fie o operație de rutină, ea putând crește procentul de morbiditate postoperatorie, beneficiul terapeutic fiind redus. Opiniem pentru limfadenectomia aortică distală, în jurul și imediat deasupra bifurcației, în condițiile în care explorarea intraoperatorie suspicionează invazie ganglionară pelvină ori para-aortică (ganglioni mari și de consistență crescută).

Deși există posibilitatea invaziei directe în ganglionii para-aortici fără ca cei pelvieni să fie implicați, această posibilitate este totuși extrem de rară.

Există o serie de studii care atestă o interesare redusă a ganglionilor para-aortici la pacientele cu cancer cervical aflate în stadiile IB si IIA. Astfel, Podczaski și colab. la un lot de 52 paciente, găsesc o interesare a ganglionilor para-aortici într-un procent de 13,4%, cu mențiunea că la 53,8% dintre paciente, tumora cervicală avea un diametru mai mare de 5 cm [19].

Patsner și colab. recoltează mostre de ganglioni para-aortici la 125 de paciente cu cancer de col uterin aflate în stadiul IB (cu tumori ≤ 3 cm), gasind o invazie a acestor ganglioni la numai 1,6% dintre acestea [20]. Aceste paciente prezentau micrometastaze în ganglionii para-aortici recoltați, dar și ganglionii pelvieni erau masiv invadați.

Extirparea ganglionilor para-aortici sau a unor mostre din aceștia, are în special valoare prognostică, permițând identificarea pacientelor cu risc crescut de persistență a bolii și care pot beneficia de radioterapie adjuvantă postoperatorie la nivelul pelvisului cu extensia câmpului de iradiere și la nivel para-aortic. Un studiu efectuat de Downey și colab. în 1989 aduce dovezi indirecte asupra faptului că iradierea pelvină postoperatorie este mult mai eficientă în scăderea riscului de recidivă și în controlul asupra bolii după ce limfadenectomia pelvină a îndepărtat ganglionii clinic invadați [21].

Astfel, pacientele cuprinse în acest studiu, la care au fost îndepărtați ganglionii pelvieni metastatici și care au fost supuse unei radioterapii postoperatorii pe un câmp extins, au prezentat o rată a absenței recurențelor la 5 ani de 51%.

Studiul efectuat de Polish și colab. în același centru a arătat că la 84% dintre pacientele cu cancer cervical aflat în stadiile IB și IIA, ganglionii pelvieni invadați au putut fi extirpați și nici una dintre pacientele la care acest lucru nu a fost posibil nu a supraviețuit la 5 ani [22].

Rata de supraviețuire cu absența recidivelor la 5 ani a fost asemănătoare pentru pacientele prezentând numai micrometastaze ganglionare pelvine (56%) respectiv pentru cele cu ganglioni pelvieni masiv invadați (57%,), ambele grupe de paciente fiind supuse radioterapiei în aria pelvină și para-aortică [19].

Radioterapia și eventual chimio-terapia urmate de rutină sau în cazuri selectate, de histerectomie radicală

La pacientele prezentând tumori cervicale mari (> 4 cm) sau la cele cu risc anestezic și chirurgical crescut, se recomandă terapia radiantă de prima intenție sau ca tratament exclusiv.

Din păcate sunt puține studiile care analizează indicația și beneficiul tratamentului chirurgical aplicat in urma radioterapiei.

Un studiu randomizat a fost realizat de Perez și colab. în 1987 pe două loturi de paciente cu cancer cervical aflat în stadiile IB și IIA, un lot fiind supus numai radioterapiei, în timp ce la al doilea lot radioterapia a fost urmată de intervenția chirurgicală radicală (histerectomie radicală și limfadenectomie pelvină) la 4-6 săptămâni după încheierea terapiei radiante [23].

Studiul nu a evidențiat diferențe semnificative privind supraviețuirea, cu absența semnelor de boală, la 5 ani între cele două loturi (89% la pacientele supuse terapiei radiante exclusive și 80% la cele la care radioterapia a fost urmată de intervenția chirurgicală). Acest studiu a exclus, însă, pacientele cu tumori cervicale mai mari de 5 cm.

Un alt studiu de amploare efectuat de GOG (protocolul 71) a comparat rezultatele radioterapiei pelvine și intracavitare urmate sau nu de histerectomia radicală [22]. Datele parțiale ale acestui studiu atestă faptul că intervenția chirurgicală îmbunătățește controlul local al bolii, dar nu influențează supraviețuirea la distanță. Trialul a fost apoi extins prin asocierea la radioterapie a chimioterapiei concomitente (cisplatin 40 mg/m^2 săptămânal) versus radioterapie singură, ambele forme de tratament fiind urmate la 3-6 săptămâni de histerectomie radicală [24]. Rata de supraviețuire la 3 ani a fost mai mare în cazul primului lot de pacienți (asociere radio- și chimioterapie) 83% față de numai 74% la pacientele care au primit radioterapie singură.

Radioterapia exclusivă este rar recomandată și se justifică atunci când există contraindicație pentru intervenția chirurgicală. Constă în iradiere externă primară la nivelul pelvisului urmată de brachyterapie, dozele folosite depinzând de volumul leziunii, de răspunsul leziunii la tratamentul radiant, de anatomia și geometria pacientei, precum și de preferința oncologului radioterapeut.

Echilibrul dintre dozele de radiații necesare distrugerii leziunii și excesul de radiații care poate afecta țesuturile și structurile de vecinătate (vezica urinară, vaginul, rectul) este uneori dificil de realizat. În ultimii ani, s-au realizat programe computerizate în care sunt introduse rezultatele explorărilor imagistice (CT scan , RMN etc.) și care permit calcularea unor doze optime de iradiere în funcție de volumul tumorii și de țesuturile adiacente normale [25].

Chimioterapia neoadjuvantă urmată de histerectomie cu sau fără radioterapie postoperatorie

Chimioterapia neoadjuvantă are rolul de a reduce volumul tumorilor cervicale semnificative, crescând astfel rata rezecabilității tumorale. Există mai multe studii care încearcă să analizeze rolul și beneficiul chimioterapiei neoadjuvante în tratamentul cancerului de col uterin.

Astfel Sardi și colab. au administrat unui lot de paciente chimioterapie neoadjuvantă (cu cisplatin, vincristina si bleomycina) în

trei cure urmate de histerectomie radicală, tehnic posibilă la toate pacientele, apoi radioterapie postoperatorie [26].

Acest lot a fost comparat cu un lot de control supus radioterapiei urmate în 85% din cazuri de histerectomie radicală. Supraviețuirea la 9 ani a fost de 80% la lotul supus chimiotearpiei neoadjuvante comparativ cu 61% la lotul de control.

Chang și colab [27]. au publicat în anul 2000 rezultatele unui studiu randomizat cu 124 paciente având cancer cervical aflat în stadiile IB și IIA recurgând la chimioterapie neoadjuvantă prin utilizarea cisplatinului, vincristinei și bleomicinei în trei cure la 10 zile interval, urmată de histerectomie radicală la 2-4 săptămâni. La 31% dintre paciente s-a recurs la radioterapie postoperatorie în condițiile unei extensii lezionale profunde în stromă sau și a invaziei parametriale. Lotul de control a fost supus numai terapiei radiante. În ceea ce privește rezultatele, nu s-au constatat diferențe semnificative statistic în ceea ce privește supraviețuirea la 5 ani, aceasta fiind de 70% la lotul supus chimioterapiei neoadjuvante și respectiv 62% la lotul de control.

În fine, un alt studiu randomizat multicentric, publicat de Benedetti Panici și colab. în anul 2002 compară eficacitatea chimioterapiei neoadjuvante cu cisplatin urmată de histerectomie radicală și eventual radioterapie postoperatorie la pacientele cu factori de risc, cu radioterapie ca unică modalitate de tratament [28]. Studiul constată o semnificativă îmbunătățire a supraviețuirii la 5 ani în cazul lotului supus chimioterapiei neoadjuvante 69% față de 51% la lotul de control.

Conlcuzii

Tratamentul cancerului de col uterin în stadiile IB și IIA rămâne un subiect controversat. Scopul principal al tratamentului, în aceste stadii, este de a maximiza probabilitatea de vindecare a leziunii în timp ce toxicitatea și riscul complicațiilor să fie redus la minimum. Marea variabilitate a schemelor terapeutice practicate în diferite centre, a căror eficacitate diferă de la un studiu la altul, nu permite identificarea unui „gold standard" în ceea ce privește cancerul cervical aflat în stadiile IB - IIA).

Conflict De Interese

Autorii nu declară niciun conflict de interese.

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Laparoscopic Cholecystectomy in Cirrhotic Patients

Marius Moraru*

Departamentul de chirurgie, Clinica I Chirurgie, Universitatea de Medicină și Farmacie "Gr. T. Popa" Iași, România

***Corresponding author:** Marius Moraru, MD, First Surgical Unit, "St. Spiridon" Hospital, Iași, Romania, Independeței Street, No 1, 700111, Iași, Romania, Tel: +40 (0) 232 21 82 72; Fax: +40 (0) 232 21 82 72: E-mail: marius.mmc@gmail.com

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Abstract

Background: Cholelithiasis is very common in cirrhotic patients (15-30%), occurring 1 to 3 times more often than in general population. The presence of cirrhosis, hepatocellular failure and/or portal hypertension increases the risk of postoperative complications in any type of surgery, especially biliary.

Methods: A review of the literature over the last 8 years (2005-2013) was performed by searching the Medline database using the following keywords "Laparoscopic Cholecystectomy" and "cirrhosis". We selected 11 studies that were considered well-documented and contained comparable data. We analyze the demographics, cholecystectomy indication and duration, incidence of perioperative complications and time of hospitalization in cirrhotic and non-cirrhotic patients.

Results: Analysis of the literature revealed a total of 842 cirrhotic patients that undergone laparoscopic cholecystectomy in group of 11 published studies. The incidence of acute cholecystitis as indication for LC (Laparoscopic Cholecystectomy) was extremely variable (3.6% to 52.38%). The ratio women to men were 1.06: 407 patients (48.34%) were men and 435 were women (51.66%). Mean of mean age reported by each series was of 53.77 years (range 21-86). Child-Pugh class was reported by 10 studies for a total of 577 patients, most of them being Child-Pugh class A (443 cases, 76.78%) and B (119 cases, 23.22%). The average operating time of reported mean values was of 94.14 minutes. Average overall morbidity rate was of 24.87%; a single study reported 75% morbidity, all other studies indicating rates of maximum 35%. The length of hospital stay was of 3.47 days (range: 1.87 to 7.2).

Conclusions: LC, although initially contraindicated in cirrhotic patients, has gradually replaced open cholecystectomy as standard surgical procedure. The operative risk in patients with liver disease depends on the degree of preexistent hepatic dysfunction, nature of the procedure and comorbid conditions.

Keywords: Cholelithiasis; Cirrhosis; Laparoscopic Cholecystectomy

Introduction

Cholelithiasis is very common in cirrhotic patients (15-30%), occurring 1 to 3 times more often than in general population. Gallstones are usually small and friable due to diminished gallbladder contractility and increased bile flow and rarely migrate thus making them frequently asymptomatic. When symptoms do occur, they are similar to those accounted in general population: biliary colic, acute cholecystitis, cholangitis. Septic complications can cause cirrhosis decompensation and thus dominating the clinical picture. The presence of cirrhosis, hepatocellular failure and/or portal hypertension increases the risk of postoperative complications in any type of surgery, especially on the biliary tree. In case of cirrhosis, the indication of cholecystectomy should be particularly weighted [1-3].

Until the middle 1990s, cirrhosis with portal hypertension represented a relative or absolute contraindication for Laparoscopic Cholecystectomy (LC). Nevertheless, the clinical complications clearly associated to cholelithiasis determined surgeons to re-evaluate the use of LC in this population group of severely affected patients.

Few publications have evaluated the benefits and safety of this procedure in cirrhotic patients so far. Most of the reports published over the last 15 years advocate for the use of laparoscopy as an alternative to laparotomy in early stages of cirrhosis.

The aim of our study is to review the literature in order to analyse the demographics, cholecystectomy indication and duration, incidence of perioperative complications and time of hospitalization in cirrhotic and non-cirrhotic patients and to compare reported data to our results.

Methods

A review of the literature over the last 8 years (2005-2013) was performed by searching the Medline database using the following keywords "laparoscopic cholecystectomy" and "cirrhosis". For the current research 11 studies considered well-documented and containing comparable data were selected. Articles with few data concerning patients' characteristics, perioperative parameters and outcome were excluded.

We independently reviewed selected studies and extracted data concerning patients' characteristics (gender, age, Child Pugh class, presence of acute cholecystitis), surgical procedure details (duration, conversion rate), postoperative evolution (length of hospital stay, morbidity, mortality, liver function deterioration, sepsis, bleeding). After extraction, data were included in a database and analyzed.

Results

Analysis of the literature revealed a total of 842 cirrhotic patients that undergone LC (Table 1). The incidence of acute cholecystitis as indication for LC was extremely variable, from 3.6% to 52.38%. Four studies did not report the indication for cholecystectomy. 407 patients (48.34%) were men and 435 were women (51.66%). The average mean age reported by each series was of 53.77 years (21-86).

Child-Pugh class was reported by 10 studies for a total of 577 patients, most of them being Child-Pugh class A (443 cases – 76.78%) and B (119 cases – 23.22%). Only two studies included patients diagnosed with Child-Pugh class C cirrhosis (4 and 2 cases, respectively).

Operating time was mentioned in 9 studies and the mean of mean values was of 94.14 minutes. The duration of the surgical procedure was extremely variable, the lowest mean time being of 65 minutes and the highest of 132 minutes.

Global morbidity rate was of 24.87%, a single study reported 75% morbidity, all other studies indicating rates of maximum 35%. Liver function deterioration, infection (pulmonary, cutaneous, peritonitis etc.), bleeding and aggravation/new onset of ascites were responsible for the majority of postoperative complications (Table 2).

As it was revealed in the analyzed studies seven (0.83%) of the 842 registered patients died. Two of the 3 papers reporting death in their study group included Child-Pugh class C patients and 5 patients belonged to this subgroup.

Mean of mean length of hospital stay was of 3.47 days (range 1.87 to 7.2 days).

Shaikh et al. [1], Pavlidis et al. [12] and Mancero et al. [13] compared laparoscopic cholecystectomy in cirrhotic versus non-cirrhotic patients and reported higher conversion rates (12.89% versus 6.5%), longer surgery time (92.6 versus 79.95 minutes), and higher morbidity rates (26.6% versus 6.89%).

Table 1: Preoperative and operative parameters in reviewed studies; n number of patients; CP Child Pugh class; AC Acute Cholecystitis.

Reference (year)	n	Gender (M/F)	Age	CP A	CP B	CP C	AC	Operative time (min)	Conversion rate (%)
Shaikh et al. 2009 [1]	20	3/17	43.9	12	8	0	NA	70.2	2 (10%)
Curro et al. 2005 [4]	42	17/25	57 (28-83)	22	16	4	22 (52.38%)	NA	3 (7.14%)
Quillin et al. 2013 [5]	94	47/47	52 (27.4-76.5)	63	20	2	2 (2%)	114 (54-270)	10 (11%)
Palanivelu et al. 2006 [7]	265	142/123	42.6 (21-86)	NA	NA	NA	93 (35.1%)	65	2 (0.75%)
Tayeb et al. 2008 [8]	30	9/21	42 (24-76)	24	6	0	NA	80 ± 26	2 (6.67%)
EL-Awadi et al. 2009 [9]	55	26/27	46.49 ± 8.6	47	8	0	2 (3.6%)	76.13 ± 15.13	4 (7.33%)
Delis et al. 2010 [11]	220	106/114	58 (28-83)	194	26	0	65 (29.5%)	95 (60-190)	12 (5.45%)
Leandros et al. 2008 [14]	34	19/15	62 (31-83)	23	11	0	8 (23.53%)	96	3 (8.82%)
Pavlidis et al. 2009 [15]	38	14/24	62.39 ± 13.26	29	9	0	7 (18.42%)	NA	6 (15.7%)
Mancero et al. 2008 [16]	30	18/12	55.13	23	7	0	NA	132	0

Table 2: Postoperative parameters in reviewed studies; LOHS Length Of Hospital Stay; LFD Liver Function Deterioration.

Reference (year)	LOHS (days)	Morbidity	Mortality	LFD	Infection	Bleeding	Ascites
Shaikh et al. 2009 [1]	2.8 ± 1.19	15 (75%)	0	NA	0	0	2 (10%)
Curro et al. 2005 [4]	7.2	15 (35%)	2 (4.76%)	NA	NA	NA	NA
Quillin et al. 2013 [5]	2.6 ± 4.3	32 (34%)	4 (4%)	NA	15 (15.96%)	1 (1.1%)	6 (6.38%)
Palanivelu et al. 2006 [7]	4	40 (15%)	0	40 (15%)	4 (1.5%)	32 (12%)	28 (10.6%)
Tayeb et al. 2008 [8]	3 ± 2.7	7 (23.33%)	0	2 (6.67%)	2 (6.67%)	2 (6.67%)	1 (3.33%)
EL-Awadi et al. 2009 [9]	1.87 ± 1.11 (1-5)	7 (12.73%)	0	3 (5.5%)	4 (7.27%)	0	NA

Delis et al. 2010 [11]	4 (2-9)	20 (11.6%)	0	NA	11 (5%)	17 (7.73%)	NA
Leandros et al. 2008 [14]	3 (1-9)	5 (14.4%)	1 (2.94%)	NA	1 (2.94%)	2 (5.88%)	NA
Pavlidis et al. 2009 [15]	4.4 ± 3.5	3 (7.8%)	0	NA	NA	2 (5.26%)	NA
Mancero et al. 2008 [16]	2.3	7 (23.33%)	0	NA	NA	1 (3.33%)	NA

Discussions

Cholelithiasis in patients with cirrhosis occurs twice as often compared to the general population. LC, although initially contraindicated in cirrhotic patients, has gradually replaced open cholecystectomy as standard surgical procedure in gallstone disease. Improvement of surgical skills and equipment has gradually allowed the use of LC in previously contraindicated circumstances including cirrhosis. Patients with liver cirrhosis have generally been considered poor candidates for LC, especially those with end-stage liver disease and portal hypertension, the latter being initially regarded as contraindications to LC. The hardness of the fibrotic liver and the augmentation of the vasculature secondary to portal hypertension with a high risk for bleeding are the major operating difficulties encountered during the procedure. Over the years, the accumulating experience in LC has resulted in an increasing number of articles reporting that LC can be safely performed in cirrhotic patients.

Despite general acceptance of this procedure in Child-Pugh class A and B patients nowadays, few data are available for patients diagnosed with class C cirrhosis. Only 2 of the 11 studies included such patients that are over-represented in mortality rate. The authors attempted LC in 3 class C patients and one of them needed to be converted to open surgery due to difficult exposure of Calot's triangle [4,5].

Data from analyzed studies show that morbidity of cirrhotic patients that undergo LC is extremely variable, between 7.8 and 75%, mostly due to infections and bleeding. In cirrhotic patients augmented perioperative blood loss is caused by a decreased production of clotting factors, a depletion of vitamin K stores, prolonged prothrombin time, an increased fibrinolytic activity, and thrombocytopenia.

Infections occur frequently in cirrhotic patients because of an immune-compromised state. As Lausten et al. showed in their study, there is an increase in circulating CD3 and CD4 cells and decrease in circulating tumor necrosis factor-α and interleukin-1β in cirrhotic patient that undergo LC [6]. Only 3 of the 11 reviewed studies considered liver function deterioration a complication of LC [7-9].

Liver function deterioration induced by anesthesia (drug toxicity, hepatic ischemia), impaired hepatic arterial circulation, perioperative hemorrhage, pneumoperitoneum, and traction on the liver is associated with ascites increase, renal failure (hepatorenal syndrome, circulatory dysfunction), and development of portal encephalopathy. The operative risk in patients with liver disease depends on the degree of preexistent hepatic dysfunction, nature of the procedure and comorbid conditions [10].

The operative risk should be carefully evaluated prior to surgery based on Child-Pugh and Model for End-stage Liver Disease (MELD) scoring system. MELD score may be superior to Child-Pugh class in assessing operative risk because it includes major components of the Child-Pugh score and also a measure of renal function, serum creatinine [11,12].

Contraindications for elective surgery include acute hepatitis, alcoholic hepatitis, and acute liver failure.

According to the reviewed literature the major difficulties encountered during LC in cirrhotic patients can be classified into 5 groups: adhesions with increased neo-vascularity, difficult retraction of the liver, inadequate exposure of Calot's triangle, a high-risk gallbladder bed and a high risk hilum [13-15].

In our opinion, left lobe hypertrophy and the irregular surface of the liver can hide the infundibulum and the cystic pedicle making surgical dissection more difficult. On the other hand, a hard and fix left lobe will obstruct view and interfere with the progression of instruments towards the cystic pedicle.

Conversion to open surgery is always an option if laparoscopic dissection proves difficult. Conversion rate decreased in the past 8 years to less than 10%. Even if conversion determines morbidity augmentation (prolonged anesthesia, increased hemorrhage and operative time) compared to laparoscopy alone, this morbidity will still remain inferior to elective open surgery.

Operative time, conversion and morbidity rate were significantly higher in cirrhotic patients versus non-cirrhotic ones, but maintained an acceptable level in all analyzed studies and also in our group. Conversion should not be considered as a failure to achieve a difficult task, but a reflection of surgical judgment, because it is meant to prevent more serious complications.

These complications include significant bleeding or biliary tract injury, leading to deterioration of liver function and sepsis. Absolute indications for conversion are not readily controlled laparoscopically bleeding and inability to define adequately the loco-regional anatomy. Uncertainty of safety and efficiency warrants an immediate conversion to laparotomy [16-18]. Usually, in these patients an infrahepatic drain is placed, because postoperative bleeding is likely in the presence of associated coagulopathy. However postsurgical drainage of the liver bed is controversial mainly because of the concern about developing ascites and secondary infection in cirrhotic patients. The manipulation of the gallbladder during surgery and a possibly decreased function of Kupffer cells and inefficient clearing of enteric micro-organisms in the postoperative period may react as contributing factors leading to secondary infection of ascites and peritonitis. Extraneous infection of ascitic fluid following a drain insertion is partly circumvented by using a closed drainage system. Drains are usually removed in 24 to 48 hours. In the postoperative period, the patients are started orally after 6 hours, unless complications are suspected. Liver function tests are carried out after 48 h. Patients are discharged as soon as they tolerate oral food and after the drain removal, within the ranges reported in the reviewed studies (1.87 to 7.2 days) and smaller than in case of

elective open surgery. Patients are referred to a medical gastroenterologist for management of cirrhosis and future follow-up.

Mortality rate proved to be acceptable in analyzed articles and was mainly due to severely altered liver function, as 2 of the 3 studies reporting death in their study group included Child-Pugh class C patients. Mortality rates as high as 76% have been reported in patients diagnosed with class C cirrhosis [2,19].

An extensive study performed by Teh et al. concluded that the most important predictors of mortality are severity of liver disease reflected by the MELD score, age, and comorbid conditions as determined by the American Society of Anesthesiologists (ASA) physical status classification. According to this author, ASA is the strongest predictor of 7 day postoperative mortality because it takes into accounts the cardiopulmonary function. MELD score is the strongest predictor of mortality beyond 7 days and long-term [12].

Advantages of Laparoscopic Cholecystectomy

In our opinion LC in cirrhotic patients offers several advantages over open cholecystectomy and includes the following [1,8,9,19,20]:

- Reduced local complications (such as wound infection, dehiscence, and postoperative hernia) due to the minimally invasive techniques of LC.
- Inadvertent bacterial seeding and contamination of the ascites is also significantly reduced, because of the less contamination of ascetic fluid during laparoscopic approach compared to laparotomy.
- The inherent magnification during LC makes easier identification and dissection of the dilated vascular channels, allowing adoption of modified surgical procedures such as subtotal cholecystectomy.
- Cirrhotic patients who are likely to be infected with hepatitis B and C pose great risk of needle stick injury to the entire operating team this risk being markedly reduced during LC.
- Coagulopathy is a major problem in patients with cirrhosis with a potential risk of bleeding in open cholecystectomy with subsequent hematoma and infection; this risk might be avoided through laparoscopic approach.
- LC offers the potential for fewer right upper quadrant adhesions postoperatively, which may be beneficial during future liver transplantation.

Conclusions

Cirrhotic patients have a higher risk of perioperative complications and require optimization prior to elective surgical intervention. Patients with well compensated cirrhosis should be considered for operative intervention when they have symptoms that may be treated surgically. LC is indicated in patients with symptomatic gallbladder stones and stable liver cirrhosis (Child A and B); for these patients the method is safe and should be the standard approach. The current general consensus revealed in the literature includes: 1) Class Child Pugh A: elective surgery well tolerated; 2) Class Child Pugh B: permissible with preoperative preparation; 3) Class Child Pugh C: contraindicated.

The laparoscopic approach has significant advantages such as easy postoperatory recovery, absence of parietal complications, short admission, and rapid social and professional recovery.

LC in patients with symptomatic cholelithiasisis is an effective and safe procedure and can be electively indicated according the experience of the operating team.

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Conflict of Interests

Author has no conflict of interests to disclose.

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Research Article Open Access

Evidence-Based Management of Sacrococcygeal Pilonidal Sinus

Aly Saber*

M.D Department of general surgery, Port-Fouad general Hospital, Port-Fouad, Egypt

***Corresponding author**: Dr. Aly Saber Department of general surgery Port-Fouad general Hospital, Port-Fouad, Egypt, Tel: +206601223752032; Fax: +20663400848; E-mail: alysaber54@gmail.com

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Abstract

A best evidence topic was arranged according to the previously accepted structured protocol. The question addressed here was if flap construction after excision of pilonidal sinus tracks showed difference in functional outcome compared to simple closure. A total of 118 papers were found using the reported search, six represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group, study type, outcomes and key results of these papers are tabulated. Of these six studies, one was one was systematic review of prospective randomized controlled trials and the other five were prospective randomized controlled studies. Four studies showed that flap construction was not superior to simple primary closure techniques in terms of outcome and patient satisfaction. The other two reported that excision and flap construction was better than excision and primary repair in treatment of pilonidal disease.

Introduction

The process of evidence- based medicine (EBM) for searching of the best available evidence for optimization of surgical practice is fundamental in every profession. The scope of EBM consists of converting the need of information for managing a particular case into a specific structured question which can be answered precisely [1]. Evidence-based practice should involve the integration of the best available research with the clinician's expertise, while also taking into consideration the patient's personal preferences and circumstances [2]. The evidence is usually retrieved from the literature. At the top of the hierarchy are systematic reviews of randomized clinical trials followed by randomized clinical trials (RCTs) [1]. A best evidence topic was constructed according to a structured protocol as described previously [3,4] as generating a clinical scenario, posing a three-part question, performing a literature search, identifying the relevant papers, appraising the papers, tabulating the results, revisiting and updating the Best Evidence Topic or (Best BET) and conclusion [4]. The optimal treatment of chronic pilonidal sinus is still a matter of debate. Excision with primary closure, either in the midline or laterally, or with the use of flaps are usually performed and compared for length of hospital stay, pain, overall cost and recurrence rates [5].

Clinical Scenario

The treating doctor is in the out-patient clinic discussing with his patient the surgical excision of the pilonidal sinus tracks with closure of the defect whether performing simple or flap closure. The treating doctor together with his team is familiar with the different surgical methods of repair and closure of the resultant defect after excision of the sinus tracks. Every patient is concerned about the two methods of closure and its outcome. He resolves to check the literature to determine if simple closure is associated with better or worse functional outcome as compared to flap closure.

Three-part question

The three-part question is composed of:

1. Patient characteristic
2. Interventions
3. Outcome [4].

In patients who undergo surgery for pilonidal sinus in case of recurrent diseases, does simple closure as compared to flap surgery improve functional outcome?

Search strategy

Using the Google scholar engine search, the following phrases were searched for: [Pilonidal sinus surgery] AND [midline OR flap closure] AND [recurrence] AND [hospitals stay] AND [wound disruption] AND [operative time] AND [complications].

Search outcome

118 papers were found using the above-mentioned phrases. Using the criteria outlined as the Best Evidence Topic or (Best BET) in a previous publication [3,4], the author selected only those papers which directly traced and compared the impact of simple closure versus flap reconstructive surgery with respect to functional outcome. This yielded a total of six papers (one was systematic review of prospective randomized controlled trials and the other five were prospective randomized controlled studies).

Results

Table I: The results of the six papers representing the best evidence to answer this clinical question are summarized in the table.

Author, date and country	Patient groups	Study type	Outcomes	Key results	Comments
Horwood et al. February 2012 UK	Keywords and MeSH terms included 'pilonidal disease', 'primary suture/ repair', 'rhomboid flap' and 'limberg/ modified Limberg flap'	Systematic review of randomized controlled trials. Level I evidence	Six studies were included for pooled analysis Two studies compared 'off-midline' primary suture with the Limberg flap repair. 641 patients were included (331 flap repairs). Rhomboid flap excision demonstrated a trend towards less disease recurrence lower wound infection and dehiscence However, no significant difference was found for pain scores, hospital stay or return to work.	P=0.07 P=0.01	This literature supports the Limberg flap-repair procedures over primary midline suture for management of primary pilonidal disease. Further high-quality studies are necessary to compare flap with primary simple repairs.
Nursal et al. February 2010. Turkey	238 patients VY flap method was compared to 2 simple primary closure techniques	Prospective randomized controlled trial Level II evidence	1- Surgical site infection 2-Early wound dehiscence without infection 3- Mean follow-up was 29.7±15.6 months. 4- Survival (time without recurrence) 5- In the whole group, independent predictors of recurrence according to logistic regression analysis were younger age, recurrent disease, presence of discharge on physical examination, and development of postoperative surgical site infection.	NS (P =0 .129) NS (P =0.665) NS (P =0 .648)	VYAF is not superior to simple primary closure techniques in terms of outcome and patient satisfaction. For most cases, simple primary closure would suffice.
Muzi et al. Junly 2010 Italy	260 patients Limberg flap procedure or tension-free primary closure.	prospective, standard procedure, controlled, randomized, single-center clinical trial Level II evidence	1-Success of surgery was achieved in 84.62% of Limberg flap versus 77.69% of primary closure. 2- Surgical time for primary closure was shorter. 3- Wound infection was more frequent in the primary closure 4-postoperative pain 5- time off from work and wound dehiscence. 6-Recurrence	NS (P =.079) P =0.0254 P<0.0001 P=0.672 P =0.153	Results do not show a clear benefit for Limberg flap or primary closure. Limberg flap showed less convalescence and wound infection. Primary closure was less painful, and shorter than Limberg flap.
Tavassoli et al. February 2011 Iran	100 patients group I: primary repair and group II: Limberg flap.	Prospective randomized study. Level II evidence	A--Demographic characteristics, operation time, early complication rate and recurrence. B- Return to work, first pain-free toilet sitting, pain score and patient satisfaction.	no significant difference significant difference	1-Limberg flap has similar complications as the primary repair method earlier return to work and less hospital stay, lower pain score and higher comfort and satisfaction were the advantages of the Limberg flap method. Thus, this method is recommended for the treatment of primary pilonidal disease.
Roshdy et al. October, 2010 Egypt	140 patients group I: Rhomboid flap group II: Primary closure.	Prospective randomized study. Level II evidence	1- hospital stay was longer in group II 2- return to work was faster in group I 3- postoperative complications were higher in group II 4- recurrence rate was lower in group I	(P=.009) (P=0.001) (P=0.012) (P=0.14).	Excision and rhomboid flap is better than excision and primary repair in treatment of pilonidal disease because it flattens the natal cleft, avoid dead space, healing time is short, morbidity is low, shorter

					hospital stay and low rate of recurrence.
Dass et al. August 2012 India	80 patients 1- primary midline closure 2-Limberg flap	Prospective randomized Study. Level II evidence	1- The operative time and hospital stay were longer in flap group 2- The work off period was less in flap group 3- VAS scores 4- Wound infection and disruption were less in flap group. 5-Seroma and hematoma were more in flap group. 6- Recurrence was less in flap group.	P>0.05 p=0.0048 P>0.05	The parameters in the two techniques differ significantly Rhomboid excision with limberg flap reconstruction technique surely outscores elliptical excision with primary midline closure in certain important parameters.

Discussion

The ideal method of treatment for pilonidal sinus would be one with minimal tissue loss, minimal postoperative morbidity, excellent cosmetic results, rapid resumption of daily activities, low cost, and a low recurrence rate [6]. However, although numerous operative treatment methods have been described, no treatment comprises all of these features [7].

Horwood et al. [8] systematically reviewed, by two independent investigators, six relevant randomized controlled trials for pilonidal disease regarding primary suture/repair and Limberg flap. A total of six hundred and forty-one patients were included in this systematic review. This literature supports the use of the rhomboid flap excision and the Limberg flap-repair procedures over primary midline suture techniques for the elective management of primary pilonidal disease but further high-quality studies are necessary to support this. The points of strength of this paper are being belonged to level I as a systematic review of randomized trials or n-of-1 trials according to the latest Oxford Level of Evidence [3,4] and the randomized trials with poor methodology were excluded.

Nursal et al. [9] in their prospective randomized controlled study compared the V–Y advancement flap (VYAF) versus 2 simple primary closure techniques. VYAF was not superior to simple primary closure techniques in terms of postoperative complications, recurrence, and patient satisfaction and for most cases, simple primary closure would suffice. Although theoretically appealing, the VYAF technique does not offer any advantages compared to the simpler primary closure techniques. VYAF technique, however, may be needed especially in patients with large defects that cannot be mechanically approximated with primary closure. This paper reported that independent predictors of recurrence according to logistic regression analysis were younger age, recurrent disease, presence of discharge on physical examination, and development of postoperative surgical site infection. Points of strength of this paper were the sample size and the operating surgeons. According to the layered chi-square analysis, there was no difference between the type of surgery and recurrence as layered across the surgeons. Also, the results were well-tabulated and the probability values of significant were traced.

In a prospective, standard procedure, controlled, randomized, single-center clinical trial, Muzi et al. [10] represented a total of 260 patients with sacrococcygeal pilonidal disease assigned randomly to undergo Limberg flap procedure or tension-free primary closure. The primary end point of the study was clinical evidence of complete wound healing at the last follow-up evaluation without occurrence of wound infection, wound dehiscence, and sinus relapse, which were considered treatment failures. The end point has been tested using a logistic regression model, exploring the effect of the surgical procedure adjusting for age, sex, and initial presence of either acute or chronic infection. Secondary end points were days of confinement in bed, pain VAS score, and time off from work. These results did not show a clear benefit for surgical management by Limberg flap or primary closure. Limberg flap showed less convalescence and wound infection; our technique of tension-free primary closure was a day case procedure, less painful, and shorter than Limberg flap. The sample size and the independent observer were two points of strength. An independent observer, who was not from the surgical team and who was unaware of the treatment assignments, recorded all data, which included postoperative events and follow-up findings.

Tavassoli et al. [11] performed excision with primary repair as group I and rhomboid excision with the Limberg flap as group II. The demographic characteristics of their patients, early and late complications, comfort and pain score on the first and fourth postoperative day, hospital stay, time of return to work, and patient satisfaction were compared. There was no significant difference between the two groups in terms of demographic characteristics, operation time, early complication rate and recurrence. But significant difference was observed in return to work, first pain-free toilet sitting, pain score and patient satisfaction. The authors concluded that the Limberg flap has similar complications as the primary repair method, but earlier return to work and less hospital stay, lower pain score and higher comfort and satisfaction were the advantages of the Limberg flap method. Thus, this method is recommended for the treatment of primary pilonidal disease. The relatively smaller number of patients was a weak point of this paper otherwise the results were well-tabulated and the probability values of significant were traced.

Roshdy et al. [12] performed rhomboid flap versus primary closure after excision of sacrococcigeal pilonidal sinus as Prospective randomized study in 140 patients. The authors stated that goal for treatment of pilonidal disease in 2 fold, the first is excising and healing with low rate of recurrence the second is minimizing patient inconvenience and morbidity after surgical procedure. In conclusion the excision and rhomboid flap is better than excision and primary repair in treatment of pilonidal disease because it flattens the natal cleft avoid dead space, healing time is short, morbidity is low, shorter hospital stay and low rate of recurrence. In this paper, the sample size

was satisfying the results were well-written and well-tabulated and the probability values of significant were traced.

A prospective randomized study of 80 patients of sacrococcygeal pilonidal sinus was performed By Dass et al. [13] using elliptical excision with primary midline closure versus rhomboid excision with limberg flap reconstruction. Data was compiled in terms of operative period required, immediate post-operative complications, post-operative pain (VAS scores), work-off period, hospital stay and recurrences over a follow up of 3 years for the two study groups. Data thereby collected was analyzed by using Microsoft excel. The parameters in which the two techniques were found to differ significantly were work-off period, immediate post-operative complications profiles and recurrence rates. Rhomboid excision with Limberg flap reconstruction technique surely outscores elliptical excision with primary midline closure in certain important parameters. This study was limited by the smaller sample size which was considered a weak point of this paper.

Clinical bottom line

Although different surgical approaches have been used to manage sacrococcygeal pilonidal sinus, none of these approaches eliminate the postoperative morbidity and there is no agreement on the gold standard surgical treatment. Any procedure should stress well on other parameters than postoperative morbidity and recurrence such as technical simplicity, hospitalization period required, and off work period. Comparative studies of the various procedures are being increasingly published for documenting the relative superiority of one over the other. For simple non-recurrent pilonidal sinus, less invasive surgery with limited excision and primary closure could be enough.

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Research Article Open Access

In Patients Who Underwent Total Thyroidectomy Some Non-Steroidal Anti-inflammatory Drugs Effects on Thyroid Replacement Therapy

Süleyman Kargin[1*], Didem Tastekin[2], Azamet Cezik[3], Murat Cakir[1], Kemal Kılıç[4], M Sinan Iyisoy[5] and Tevfik Küçükkartallar[1]

[1]*Necmettin Erbakan University, Meram Medical Faculty, Department of General Surgery, Konya, Turkey*

[2]*Necmettin Erbakan University, Meram Medical Faculty, Department of Medical Oncology, Konya, Turkey*

[3]*Çorlu State Hospital Çorlu, Tekirdağ*

[4]*Kartal State Hospital, Department of General Surgery, İstanbul, Turkey*

[5]*Necmettin Erbakan University, Meram Medical Faculty, Department of Statistic, Konya, Turkey*

[*]**Corresponding author**: Süleyman Kargin, Konya University, Meram Medical Faculty, Department of General Surgery, Konya- 42080, Turkey, Tel: 90 332 2236123; Fax: 90 332 2236182; E-mail: drs.kargin@hotmail.com

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Abstract

Objective

Non-steroid anti-inflammatory drugs can change serum thyroid hormone concentrations by binding to serum proteins. If misunderstood, this situation can give way to inappropriate diagnoses and faulty treatment planning for thyroid diseases in clinical practice. The purpose of our study was to investigate the effects of ketoprofen, lornoxicam, and etofenamate, which are frequently used in clinical practice, on thyroid function tests.

Methodology

The study covered 28 rabbits divided into 4 groups. Groups were administered intramuscular injections daily for 10 days. Thyroid hormones concentrations were tested in the blood samples end of day 10.

Results

An increase in free thyroxin level in the lornoxicam group was recorded on day 7 in comparison to other groups (p=0.015). There was a statistical decrease regarding thyroid stimulant hormone concentration after day 5 in all three groups (Day 5 p=0.000, day 7 p=0.003, day 10 p=0.00).

Conclusion

We believe that previous history of non-steroid anti-inflammatory drug use should be taken into consideration within the scope of patients' anamneses because non-steroid anti-inflammatory drug use can change the results of thyroid function tests and this change may lead to misevaluations and mistreatment not only for patients with thyroid diseases but also for normal patients.

Keywords: Thyroid function; Non-steroidal Drugs; Thyroxin

Introduction

Many drugs affect the results of thyroid function tests. There are many target areas for the interaction of drugs in thyroid hormone synthesis, transport, metabolism, and absorption. Most of triiodothyronine (T3) and tetraiodothyronine (thyroxin=T4) are carried in circulation by binding to proteins like albumin and transthyretin. A very small portion of thyroid hormones (about T3=0.3%; T4=0.03%) are found free in the circulation and carry out biological activities.

Non-Steroidal Anti-Inflammatory Drugs (NSAID) especially affects the binding areas of thyroid hormones' serum proteins and temporarily increases serum thyroid hormone levels. This, in turn, suppresses serum thyroid stimulant hormone (TSH) levels [1,2]. If this condition is misunderstood, the changes that are brought about by drugs can lead to inappropriate diagnosis and faulty treatment planning.

Ketoprofen is a propionic acid derivative. They bind especially to albumin, a serum protein, at a high rate (99%). Lornoxicam is a non-selective NSAID within the oxicam group with analgesic, anti-inflammatory, and antipyretic effects. The reason why Lornoxicam is more attractive than other NSAID drugs in post-op pain treatment is based on the fact that it has a good tolerance profile because of its short half-life, that it has few side effects, and that it has a repeatable dose. Etofenamate has been used as analgesic and anti-inflammatory drug for years. There has been an increase in pre-op and post-op etofenamate use in recent years. Its effect on pain resembles fentanyl and can safely be used [3].

The purpose of this study is to investigate the effects of three NSAIDs, which are being frequently used in daily practice and frequently prescribed, on rabbits' thyroid function tests.

Methodology

Rabbits

The study was conducted upon the consent (2012-45) of Konya Necmettin Erbakan University, Meram Medical Faculty, Experimental Medical Research and Implementation Center's Board of Ethics. The study covered 28 New Zealand rabbits of average age and weight. The rabbits were randomly classified into four groups: Group 1 (control group), Group 2 (Ketoprofen group), Group 3 (Lornoxicam group), and Group 4 (Etofenamate group). The rabbits were administered antiparasitic drugs before the trial and it was determined that they were perfectly healthy clinically. The animals were fed *ad libitum* by pellet feed twice daily (08:00 and 20:00 h) for ten days and enough clean water was provided.

Trial Procedure

The experimental animals were equally classified into 4 groups. These were: Group 1 (Control group), Group 2 (Ketoprofen group), Group 3 (Lornoxicam group), and Group 4 (Etofenamate group). The ketoprofen (n=7) (Profenid ampoule, Sanofi Aventis) group received once a day intramuscular injection of 2 mg/kg, the lornoxicam group (n=7) was administered (Xefo vial, Nycomed ASK) once a day intramuscular injection of 0.2 mg/kg, and the etofenamate group (n=7) (Flexo ampoule, SantaFarma) was given once a day intramuscular injection of 15 mg/kg of their respective drugs for 10 days (Table 1). The control group, on the other hand, was injected 0.3 mg/kg 0.9% normal saline solution intramuscularly.

Table I: The types of pharmacological agents used their amounts, administration manners, administration frequency, and action time.

Pharmaco-logical Agents	Dose	Admin-istration Manner	Volume	Admin-istration Frequency	Action Time
Ketoprofen	2 mg/kg	I.M.	0.04 ml	Daily	24 Hrs
Lornoxicame	0.2 mg/kg	I.M.	0.1 ml	Daily	24 Hrs
Etofenamate	15 mg/kg	I.M.	0.06 ml	Daily	24 Hrs
%0.9 Saline	0.3 mg/kg	I.M.	0.2 ml	Daily	24 Hrs

During the course of the study, drug administration was carried out every morning at 08:00. Twenty four hours after the first drug administration and before feeding, when the rabbits were hungry, 2 cc of blood was duly drawn from all the animals' vena auricularis into heparinized Eppendorf tubes at 07:00. The samples taken were immediately analyzed by (using Olympus commercial kits) in an Olympus autoanalyzer. Drug administrations were repeated in the same dosage every 24 hours appropriate to each group. On days 2, 3, 5, 7, and 10 cc of blood samples were drawn from the rabbits using the same method at 07:00. Free T3 (FT3), free T4 (FT4), and TSH levels were tested in all the blood samples.

Statistical Analysis

The values were given as mean ± standard deviation and the data collected were compared by using ANOVA and Tukey's HSD (honestly significant difference) tests and covariance analyses. All the statistical analyses were conducted with SPSS 10.0 for Windows package program. Statistical differences were evaluated according to the $p<0.05$ level.

Results

No mortality cases and side effects were seen in any group during the course of the study. The changes in FT3, FT4, and TSH levels obtained during drug administration are shown in Table 2.

A significant increase in the FT4 level on day 7 of the treatment was seen in the lornoxicam group in comparison to the control group ($p<0.015$). Although there was some increase in FT3 levels in all groups during the study, no statistically significant increase was observed among the groups.

Further, a significant decrease in TSH levels was observed after the 5th day among the ketoprofen, lornoxicam, and etofenamate groups (day 5: $p=0.000$, day 7: $p=0.003$, day 10: $p=0.00$). While TSH<10 μIU/ml in all the 35 samples from the control group, TSH ≤ 10 μIU/ml in 31 out of 104 samples from the ketoprofen, lornoxicam, and etofenamate groups. TSH was found to be TSH ≤ 10 μIU/ml (46.7%) in 29 out of 62 samples studied on day 5 and later during the course of the treatment in these three groups.

TSH levels in ketoprofen, lornoxicam, and etofenamate groups started to decrease after the first 24 hours in comparison to the control group but statistically significant decrease was seen in all these three groups on day 5 ($p<0.015$). While this decrease in TSH levels continued on days 7 and 10 in the ketoprofen and lornoxicam groups, the significance was lost in the etofenamate group on day 7, only to come back on day 10 ($p<0.05$). Moreover, the FT4 level was significantly elevated only in the lornoxicam group on day 7 in comparison to the control group. It persistently continued after day 7. No significance was observed, however, in FT3 levels in all three groups in comparison to the control group.

While FT4 concentrations were at an average of 17.5 μg/ml (mean 17.2-17.8 μg/ml ± SD) during the whole course of the study in the control group, FT4 concentrations were at an average of 20.4 μg/ml (mean 16.8-23.4 μg/ml ± SD); 23.6 μg/ml (mean 20.1-25.4 μg/ml); and 22.3 μg/ml (mean 21.09-24.8 μg/ml) for the ketoprofen, lornoxicam, and etofenamate groups, respectively (Table 2).

Table II: The effects of Ketoprofen, Lornoxicam, and Etofenamate on thyroid function tests (mean+SD) ($p<0.05$).

Parameter	Days (n=27)					
	Group	1	3	5	7	10
	Control	12.00 ± 1.00	11.86 ± 1.34	11.57 ± 1.90	11.14 ± 1.57	11.67 ± 1.21

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Free T3 pmol/L	Keto	10.83 ± 0.98	12.29 ± 0.75	12.00 ± 3.31	12.50 ± 1.22	13.57 ± 2.14
	Lorn	10.86 ± 1.06	12.14 ± 0.90	13.14 ± 0.90	13.14 ± 2.11	13.14 ± 2.41
	Eto	11.29 ± 1.25	11.14 ± 1.46	11.71 ± 0.75	12.29 ± 1.60	12.71 ± 3.45
	Total	11.20 ± 1.11	11.86 ± 1.17	12.11 ± 1.98	12.26 ± 1.74	12.81 ± 2.43
Free T4 pmol/L	Control	17.40 ± 0.54	17.71 ± 4.30	17.86 ± 3.07	17.14 ± 4.22	17.83 ± 1.94
	Keto	16.67 ± 5.08	19.71 ± 6.34	20.29 ± 4.49	22.17 ± 4.95	23.29 ± 6.52
	Lorn	20.00 ± 4.20	23.43 ± 5.88	24.14 ± 2.96	25.43 ± 3.86	25.14 ± 3.33
	Eto	21.14 ± 5.90	22.14 ± 6.14	22.29 ± 4.68	21.57 ± 4.42	25.00 ± 7.39
	Total	19.00 ± 4.69	20.75 ± 5.84	21.14 ± 4.36	21.56 ± 5.11	23.00 ± 5.85
TSH µIU/ml	Control	11.400 ± 054	11.57 ± 0.53	11.71 ± 0.48	11.42 ± 0.53	11.83 ± 0.40
	Keto	11.233 ± 0.25	10.64 ± 0.69	10.37 ± 0.38	10.28 ± 0.91	10.21 ± 1.06
	Lorn	11.129 ± 0.34	10.61 ± 0.67	10.22 ± 0.47	9.77 ± 0.91	9.58 ± 0.29
	Eto	11.443 ± 0.52	11.08 ± 0.62	10.71 ± 0.75	10.57 ± 0.53	10.18 ± 0.91
	Total	11.29 ± 0.42	10.97 ± 0.71	10.75 ± 0.78	10.52 ± 0.93	10.40 ± 1.08

It was observed that the drugs administered to the groups, except for the control group, had effects on FT4 and TSH levels. The lornoxicam group, however, proved to be the only group which had significant increase in FT4 levels among the groups studied. Further, it has more effects on FT4 and TSH levels. Etofenamate is less effective on thyroid function tests in comparison to the others among the groups studied. No significant effect of the drug on the FT3 levels of the groups was found.

Discussion

NSAIDs have been used in pain treatment since ancient ages. Awareness about the risks and side effects of the NSAIDs, however, has recently been on the rise [4]. These types of drugs are prescribed for all painful conditions especially for joint pain and headaches. It has been reported that lornoxicam provided better pain control during the follow-ups after oral surgery and thyroidectomy and had a longer action time [5]. NSAIDs do not only have hepatic side effects but also gastrointestinal, cardiovascular, renal, hematological, and endocrinological side effects.

Drug use may have *in vitro* or *in vivo* effects on thyroid tests and/or thyroid functions [6]. Drugs affect thyroid functions by changing the TSH level through affecting thyroid hormone secretion or hormone metabolism. While some drugs lead to TSH suppression by decreasing TBG concentration or decreasing the binding of FT4 to TBG, some others cause an elevation in TSH levels by bringing about an increase in TBG [7].

Subclinical hyperthyroidism is defined as the case where TSH level is low while FT3 and FT4 are observed in normal concentrations in the presence of drug use that inhibits TSH secretion like hypothalamic or hypophyseal disease or glucocorticoid and dopamine [8]. The prevalence of subclinical hyperthyroidism in the general public is about 3% and this rate increases for male and female patients who are over 65 years of age [9]. It is generally seen in relation to endogenous reasons. It has been shown that some NSAIDs changed the results of thyroid function test in human beings because the thyroid hormones in circulation bind to serum binding proteins at a high rate and various NSAIDs may change the binding areas of thyroid hormones on serum proteins [2,10, 11]. Through the inhibition of 5' deiodinase enzyme in peripheral tissues, the transformation of Thyroxine (T4) into Triiodothyronine (T3) can be changed [12,13]. When there are abnormalities in thyroid binding proteins, the free functions of thyroid hormones reflect their physiological effect better than their total fractions [14]. Thus, miscalculations can be made in the measurement of thyroid hormones in blood. In studies conducted with humans, it has been shown that NSAIDs had significant effects on thyroid functions and that they led to wrong thyroid results and wrong treatment decisions [15,16]. There are many articles which demonstrated that treatment with salicylates in therapeutic doses in the short term caused increases in serum free thyroid hormone concentration and suppression of TSH. The FT4 level can vary due to the use of various non-steroids [2,17]. Some studies reported that drugs which have a similar effect like indomethacin and diclofenac sodium, meclofenamic acid, fenclofenac, phenylbutazone, ibuprofen, and paracetamol increased free T3 and T4 levels by inhibiting the binding of T3 and T4 to plasma proteins [18-23]. For instance, there is an article which showed that a single dose of aspirin use acutely increased free thyroid hormone level by 2-3 times [24]. In our study we investigated the effects of ketoprofen, lornoxicam, and etofenamate, which we frequently use in clinical practice, on thyroid function tests. It was seen that an increase started in the groups within the first 24 hours. The FT4 level, however, was significantly elevated only in the lornoxicam group on day 7. On the other hand, TSH suppression was observed in the ketoprofen and lornoxicam groups on days 5, 7, and 10 while it was observed on days 5 and 10 in the etofenamate group.

TSH is the first thyroid function test referred to by clinicians. Studies have shown that TSH is both a rapid and inexpensive diagnostic method in showing the right diagnosis [25]. Abnormal TSH level in patients receiving thyroxin treatment points out to inadequate treatment or overdose treatment. The main hormone responsible for thyroid functions in the body is T3. The fact that T3 levels are within normal limits although thyroxin is low may be enough for cases to maintain thyroid functions. T4's capacity for serum binding decreases as a result of the increase in environmental transformation, thus, FT3 values are generally observed to be normal. TSH is used only for initial screening in many clinics because it has a high sensitivity level for thyroid functions. The use of only FT3 and FT4 results are not recommended because they cannot determine subclinical thyroid dysfunctions. Therefore, it would be more appropriate to study FT3 and FT4 concentrations of TSH in combination to evaluate thyroid functions. FT3 levels in our experimental animals were within normal limits and no significant difference was found between the study groups and the control group. This result was in line with literature. The increase in environmental T4's transformation into T3 can be regarded as the reason for this result [24]. Early changes in TSH concentrations and later changes in FT4 concentration, the determination of TSH alongside with FT4 level support the idea that thyroid function tests can be more safely evaluated. FT4 was significantly elevated in the lornoxicam group on day 7 of treatment in comparison to the control group. This difference is more pronounced in the treatment with lornoxicam in comparison to the ketoprofen and etofenamate groups.

In conclusion, since NSAIDs are commonly used in clinical practice and prescribed by all physicians for different reasons, we believe that the use of these drugs may lead to changes in thyroid function tests, may cause misunderstandings especially in the cases of individuals with no thyroid problems, and may also lead to wrong dose regulation for the L-thyroxin drug used by patients with previous history of total thyrodectomy procedure. Specifically when the thyroid function tests of such patients are evaluated, their NSAID histories should also be evaluated and should be taken into consideration when initiating treatment. Our study covered the 10-day treatment follow-up of animals which were administered three non-steroid drugs. We, however, think that such studies should cover a longer period of time and the drugs' effects on humans should also be investigated.

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Research Article Open Access

Nonintubated Videothoracoscopic Operations in Thoracic Oncology

Tommaso C Mineo* **and Federico Tacconi**

Thoracic Surgery Division, Tor Vergata University, Italy

***Corresponding author**: Dr. Tommaso C Mineo, Thoracic Surgery Division, Tor Vergata University Floor 7th, Viale Oxford 81, 00133, Rome, Italy, Tel: 0039 06 20902880; Fax: 0039 06 20902881; E-mail: mineo@uniroma2.it

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Abstract

Background: Despite general anesthesia with one-lung ventilation represents the standard to perform thoracic surgery operations, there is an increasing interest toward alternative methods, such as the use of local or neuroaxial analgesia alone in fully alert or mildly sedated patients. These can be applied to perform a series of videothoracoscopic procedures.

Material and Methods: We reviewed our own institutional experience with this kind of surgery, as well as the most relevant literature findings available on this topic at the usual search websites (PubMed, Scopus, EMBASE). We focused on more recent advances regarding indications, expected advantages, possible pitfalls and implications for future research.

Results: Such an operative modality can be safely and successfully adopted to manage a series of common malignant and non-malignant diseases. In thoracic oncology, it is mainly employed to treat malignant pleural effusion, to remove of pulmonary lesions of any origin, and to perform mediastinal biopsies. Furthermore, even complex procedures such anatomic lung resections and thymectomy are now being performed in this way. When taking into the account just intermediate to major surgeries, reported conversion rates to general anesthesia range between 2.8 and 9%. Despite the lack of randomized controlled trial, there is a general perception that non-intubated videothoracoscopic operation may translate into a lower morbidity rate, better hematosis, and preserved perioperative immunosurveillance. No sufficient data is available as far as long-term outcomes are concerned.

Conclusions: Non-intubated videthoracoscopic operations may be as effective as the equivalent procedures performed with general anesthesia, while providing advantages in terms of cost and postoperative morbidity. This surgical practice should thus be included in the armamentarium of modern era thoracic surgeons, and appropriately designed studies should be undertaken to better define its merits and limitations.

Keywords: Regional anesthesia; VATS; non-small cell lung cancer; lung resection; pulmonary metastasecomy; mediastinal masses; pleural effusion

Introduction

With the advent of the patient-centered health care concept, there is an increasing attention to minimize at most the global invasiveness of surgical performances, while maintaining an unaltered level of safety and effectiveness. In recent years, this need has driven an outstanding development of minimally-invasive operative modalities, which are now the accepted standard to perform a broad spectrum of thoracic operations. Meanwhile, the advances in anesthesiology practice have given a further contribution to the improvement of postoperative outcomes, particularly thanks to the widespread diffusion of regional and neuraxial techniques. The latter are usually adopted in combination with general anesthesia, whit the purpose of achieving better postoperative pain control, attenuated response to surgical stress, and reduced dosage of intravenous or volatile anesthetic drugs. Yet, regional anesthesia can be also used as a standalone tool to carry out thoracic operations in spontaneously ventilated patients, thus obviating the need of general anesthesia and orotracheal intubation [1-5]. This operative modality, which has been also named as “awake” or “non-intubated” thoracic surgery, is now gaining increasing acceptance is some institutions, even though there is no definitive consensus in terms of indications, possible advantages, and pitfalls (Table 1). In this article, we review the basic concepts of this kind of surgical practice, with special focus on its applicability to the specific subset of oncology diseases (Non-Intubated Thoracic Oncology Surgery, NITOS).

Main PROS
Avoidance of GA and OLV related adverse effect
Reduced postoperative morbidity/shorter hospitalization
Improved quality of recovery
Time and cost saving advantages
Non-inferior efficacy versus standard approaches
Possible anticancer activity (↓ perioperative cortisol release → preserved NK activity)
Main CONS
TEA-related side effects to be taken into the account when used
Lack of evidence-based support

More difficult surgical technique → specific training mandatory
Patient safety questionable

Table I: Hypothesized Pros and Cons of NITOS operations. GA: general anesthesia; NK: Natural-killer; OLV: One-lung ventilation; TEA: Thoracic Epidural Anesthesia.

Material and Methods

General Principles

The basic idea of NITOS is that a global drop of perioperative morbidity rate could be obtained by avoiding a series of injurious effect and complications related to general anesthesia and One-Lung Ventilation (OLV). This consideration mainly applies to patients with composite comorbidity status, who are more prone to develop postoperative adverse events.

It is well known that OLV in itself, regardless of surgical manipulations, may induce inflammatory changes at the level of small airways and lung parenchyma, through diverse mechanisms [6-22]. The latter include elevated positive pressure (barotrauma), alveolar overdistension (volutrauma) [8,10], repetitive collapse-reopening cycles (atelettrauma) [10], low oxygen tension, and the so-called reventilation injury [13,14,22]. All these factors are responsible for oxidative stress [16,19,20,21] and excess recruitment of inflammatory cells, with subsequent activation of cytokine network and establishment of an inflamed microenvironment [8,11-13,15]. These compartmental changes, which can involve both the dependent and non-dependent (operated) lung, configure a condition known as "Ventilator-Associated Lung Injury" (VALI). The latter leads, in turn, to interstitial edema [12,14,16], loss of surfactant [11,12], ventilation-to-perfusion mismatch, and decreased lung compliance [11,12]. These effects occur in a time-dependent manner, as they increase remarkably after 1-hour of OLV [20]. In most instances, VALI can remain clinically silent, or be responsible for just transient and mild respiratory impairment. In patients with preexisting lung diseases, however, VALI may evolve to frank acute lung injury according to the so-called double-hit paradigm. This severe complication can occur in nearly 4% of major lung resections [17,18] and can carry a mortality rate as high as 25%. Excess fluid administration [18], pain, phlegm retention, and atelectasis are common factor which can participate to worsen this clinical scenario.

Systemic effects of VALI can also be seen, and are likely mediated by spillover of proinflammatory cytokines to the blood circulation [23]. They include liver injury [23], natural-killer cells (NK) impairment [24], and cardiac arrhythmias [25]. Despite these complications are usually self-limiting and well treatable, they can trigger potentially life-threatening deterioration in more fragile patients.

Other common adverse effects of general anesthesia in thoracic patients include acute kidney injury, diaphragmatic failure, postoperative cognitive impairment, and tracheobronchial rupture. Despite the latter has been estimated to occur with a relatively low rate (1/20.000), it may be life-threatening in more than 20% of istances [26].

Surgery, anesthesia and cancer progression

Another matter of investigation is as to whether the employ of locoregional techniques, alone or in combination with general anesthesia, can modify the biological behavior of cancer cells, thus affecting postoperative outcomes. In this regard, it is well known that both surgical manipulations and general anesthesia may interfere with tumor growth through diverse mechanisms. First, surgical stress and postoperative pain themselves may accelerate escape of occult tumor foci from their dormancy condition, thus promoting both local and distant recurrences [27,28]. This association has been proven to occur in both human and animal settings, and is mainly attributed to postsurgical suppression of immunosurveillance against tumor cells. The mechanisms undelying postoperative immune suppression, which mostly involves NK and T-helper cells, are quite complex and, probably, not fully understood. However, existing data strongly support the hypothesis of a transient dysregulation of the endocrine system leading to a dysproportionate release of endogenous steroids, alongside with a deranged cytokine production. Furthermore, the same factors may also directly promote tumor growth. In particular, circulating catecholamines, which also increase after surgery, may themselves promote tumor cell replication, migration, and expression of angiogenetic factors via an interaction with β-1 and β-2 receptors on tumor cell surface.

Some factors related to general anesthesia itself are also believed to interfere with postsurgical tumor progression [27,28]. For example, opioids seems to have a role in immune suppression, even though existing data in this regard are quite controversial. The α-2 agonist dexmedetodimine, which is being increasingly used to induce deep sedation in both surgical and ICU settings, has been shown to enhance proliferation of breast cancer cells which express the adrenergic receptor on theirs surface [29]. Other anesthetic agents that have been shown to significantly impair NK cells activity are ketamine, thiopental, and halothane [28]. Moreover, some of these are also capable to directly promote cancer growth, mainly via the induction of the so-called Hypoxia Inducible Factors (HIF), which are responsible for cancer cell survival within an unfavorable microenvironment. On contrary, propofol seems to express some anticancer activity, which has been attributed to its antiinflammatory properties, better control of surgical stress response, preservation of NK function and, again, suppression of the HIFs [28]. This is one of the reasons why propofol, alone or in combination with short-acting opioids such sufentanyl or remifentanyl, are now generally preferred to perform NITOS procedures. Mechanical ventilation and, in particular, OLV could also contribute to immunesurveillance impariment, because of its ability to promote local and systemic proinflammatory cytokine release. In this regard, Tonnesen and coworkers have found that, in patients undergoing elective thoracic surgeries, OLV in itself can reduce NK activity regardless of surgical manipulations [24].

Regional anesthesia reduces stress response to surgery by blocking afferent neural transmission, thus resulting into diminished cortisol release and attenuated systemic inflammation. Therefore, the protective role of regional anesthesia techniques against cancer progression has been thoroughly investigated. Despite the lack of prospective studies, robust evidence exists that the use epidural blockade in combination with general anesthesia can provide better oncologic outcomes in diverse cancer types. Unfortunately, much less data is available in respect to the use of local or regional anesthetics alone in NITOS. When putting these observations together, however, it appears conceivable that merging minimally-invasive surgical

technique with methods to reduce stress response and general anesthesia-related trauma might contribute to reduced likelihood of perioperative tumor progression, possibly affecting long-term outcomes. We evaluated stress hormone release, systemic inflammation biomarkers, and lymphocyte response after videothoracoscopic operations performed in awake patients with just regional anesthesia, compared to those receiving equivalent procedures performed with general anesthesia and OLV [30,31]. In the former patients, we found an attenuated cortisol release, lower postoperative C-reactive protein peak, and preserved NK and total lymphocyte count. However, these two studies were made in low-risk individuals with benign diseases, so that it is unclear whether these findings can be extended to patients with thoracic malignancies, and whether they can translate into practical benefits in the short and long term. Another criticism is that, in both these studies, epidural anesthesia was used only in the study group, a factor which could have contributed to the the observed results more than the avoidance of OLV did. To our knowledge, no other study has addressed these topics, and more robust evidence is needed to draw clearer conclusions in this regard.

Indications

NITOS operations can be indicated to perform minor to intermediate procedures in patients unfit for general anesthesia, even though healthy patients may be considered as well. So far, however, no definitive recommendation exists. In our institution, we base the decision making process on the Thoracoscore risk calculator. This simple instrument, which is available online at the Societe' Francaise de Anesthesie and Reanimation website (www.sfar.org), allows to reliably predict the risk of deadly complications after thoracic surgery procedures according to a series of parameters, including age, dyspnea, American Society of Anesthesiology, performance status ≥ 3, and composite comorbidity status. We have set a predicted risk of 2.3% as an acceptable threshold to consider NITOS as the elective approach whenever technically feasible. Major contraindications to NITOS are detailed in table 2, and mainly include conditions rendering the non-intubated procedure unsafe, oncologically unsound, or unfeasible at all. A summary of procedures we usually carry out through NITOS at our institution is provided in table 3, which also shows some changes in surgical practice occurred within the years.

Table II: Major contraindications to NITOS.

Technically demanding or oncologically inadequate procedure
Known allergy to local anesthetics
High risk for intraoperative seizure (brain metastases)
Patient “not keen” to undergo surgery with conscious sedation
Impaired patient ability to cooperate
Past medical history of ipsilateral pleurisy, previous surgery or radiation therapy
Medium to severe obesity (BMI > 35)
Central hypoventilation syndrome
Hypercarbia (PaO2 > 55 mmHg)
Validated non-surgical options available
Spine deformities (if TEA to be used)
INR > 1.5 or current antiplatelets therapy

Table III: NITOS procedures at our institution: changes within years. GA: General Anesthesia; PROC: Procedure; NA: Not Applicable. * Total: represents the total number of NITOS operations. **: Ratio of total procedures performed with NITOS to total equivalent procedures performed with general anesthesia. ***: Ratio of total NITOS procedures performed with uniportal access to total NITOS procedures performed with multiportal thoracoscopic access.

PROC	2002-2007			2007-2014		
	Total*	NITOS vs. GA **	Uniportal vs. multiportal ***	Total*	NITOS vs. GA **	Uniportal vs. multiportal***
Wedge resections/ metastasectomy	32	41%	10%	76	72%	62%
Anatomical segmentectomies	1	NA	NA	31	76%	8%
Pleural effusion	86	64%	76%	112	86%	98%
Mediastinal biopsy	12	>70%	62%	11	>68%	100%

Technical issues

A series of technical considerations are mandatory to carry out a safe and effective NITOS procedure. Careful preanesthetic assessment should be made in strict cooperation with the surgical team to evaluate any possible factors leading to change of the operative plan or of the anesthesiology regimen. In particular, predictive factors of difficult intubation should be carefully evaluated. Intraoperative monitoring should include EKG, pulse-oximetry, and a radial artery catheter for real-time monitoring of blood pressure and gas exchanges. Non-invasive measurement of end-tidal CO_2 on exhaled breath through a nasal capnography may also be an useful mean, and may obviate the need of repeated arterial blood samples. Whenever necessary, the level of sedation should be titrated to provide just anxiolysis or a minimally depressed level of consciousness, while preserving airway patency and ability to respond purposefully to commands. Target-control infusion of propofol at subhypnotic dosage is frequently employed, also because of its antiemetic properties. Other sedatives, such midazolam, are adopted less frequently, due to the risk of psychomotor agitation and increased airway resistance. Amongst opioids, remifentanil is the preferred one because of the advantage of an ultrashort half-life. Should a deeper sedation be necessary, monitoring of the bi-spectral index by a dedicated sensor may help to avoid excess sedative administration. A bi-spectral index value ranging from 40 to 60 is suggested to achieve an acceptable level of sedation and areflexia, while allowing a physiological tidal breathing (12-20 per minute). However, it is desirable to have the patient able to respond to command at the end of the operation, when coughing and voluntary deep ventilation are required to allow lung expansion before wound closure. Should general anesthesia become necessary, the anesthesiology staff should be equipped to rapidly proceed with urgent orotracheal intubation. In some instance, there is sufficient time to place the put the patient in

supine position after temporary wound closure and placement of an intrapleural drainage tube. Yet, in emergent situations, double-lumen intubation with the patient lying in a lateral position cannot be avoided. If this is the case, devices such fiberoptic bronchoscope or a videolaryngoscope should be promptly available to facilitate this manoeuvre and avoid any delay, which can result in catastrophic consequences.

Pitfalls and Complications

In patients undergoing NITOS, opening of the chest is immediately followed by surgical pneumothorax with partial lung collapse. This usually allows a safe insertion of videothoracoscopic instrumentation and easy surgical manipulations, without the need of lung exclusion devices and/or intrapleural CO_2 insufflation. Furthermore, we have noted that even though spontaneous ventilation is maintained, the operated lung remains practically motionless, likely because of some hysteresis establishing after lung collapse [32,33]. In the vast majority of patients, surgical pneumothorax is well tolerated, and does not give raise to clinically relevant gas-exchange impairment. This is particularly true when dealing with patients with nearly normal respiratory function. Yet, In patients with diffuse lung disease, transient intraoperative hypercarbia may occur [1,5]. It is unclear whether this effect is attributable to surgical pneumothorax, reduced compensatory ventilation due to inhibitory effect of epidural analgesia, or sedative drug effect. This hypercarbia is usually mild (*permissive*), and practically asymptomatic in many instances. When necessary, however, it can be corrected by manual supportive ventilation via a facial mask, while the operated lung is temporarily re-expanded by placing an intrapleural tube connected to water seal. Yet, in rare instances, the hypercarbia may give rise to psychomotor agitation and even lead to a frank panic attack. Under these unfavorable circumstances, one should refrain from completing the non-intubated operation, and immediately switch to general anesthesia instead.

Adhesions might render the operation time-consuming, unpractical or completely unfeasible, so that a non-intubated procedure should be contraindicated in patients with history of pleural disease or previous ipsilateral surgeries.

Intractable cough may occur, usually as a consequence of lung manipulations leading to stretching of vagus nerve branches behind the hilum. Preventive measures include aerosolized lidocaine administration, atropine premedication, stellate ganglion blockade, and, more frequently, vagal nerve blockade by local anesthetic injection.

Some other pitfalls can be related to the anesthetic technique which is being used. Thoracic epidural anesthesia (TEA) is the most frequently adopted one, because of broad analgesic coverage of the parietal pleura which allow performing longer and more complex operations. Yet, TEA may lead to intraoperative hypotension, which should be corrected with vasopressors rather than fluid administration, in order to prevent pulmonary overload. Other possible adverse effect of TEA include impaired compensatory ventilation, bronchial constriction due to adrenergic system blockade, and reduced right ventricle adaption to increased pulmonary artery pressure [34-38], even though the relevance of these effects have not been specifically tested in the setting of non-intubated thoracic operations. TEA should also be avoided in patients with blood clotting disorders or on antiplatelet agents, due to an estimated risk of hematoma approaching 1/150.000 cases. Whenever the harm-to-benefit ratio of using TEA is into discussion, alternative measures as paravertebral infusion [39], intercostal block [40], or simple local anesthetic injection at the surgical site can be considered in an individual basis.

Results

Resection of Solitary Pulmonary Nodules

NITOS may be used to perform videothoracoscopic or open wedge resection of solitary pulmonary nodules (SPN) of unknown origin [40-48]. It can be specifically indicated to wedge out peripherally located nodules <2 cm in size, which can be easily detected and excised even in a partially inflated lung. To this purpose, both TEA and paravertebral block can be employed, as they can provide a thorough analgesic control of the targeted hemithorax. Intercostal blocks, with 1.5 ml bupivacaine at each level, can also be an option [43].

Substantially, the surgical technique does not differ from the equivalent operation performed under general anesthesia. The patient is placed in a lateral decubitus, paying attention to assure a comfortable position on the operating bed. The level of analgesia is checked before performing skin incisions by means of a pin-prick and/or a warm-cold test. If necessary, additional injection of a local anesthetic can be administered at the incision site(s). The standard approach is a 3-port videothoracoscopy. It is better to perform the first access anteriorly, on the 3rd or 4th intercostal space. At this level, the intercostal space is larger than it is posteriorly, so that a 30-degree thoracoscope may be inserted coaxially with an endoscopic grasper to allow painless lung exploration. Once the lesion is found, the other accesses can be performed accordingly to its location. The lung lesion is then grasped, and resected by means of an endoscopic stapler. An improvement of the standard techniques has been proposed by Tseng and coworkers, who employed a dedicated "needlescopic" instrumentation through 3-mm skin incisions [44]. Lesser et al. used a two-access method with 2 and 11-mm openings and the use of a laser device to excise the nodules [46]. Alternatively, the operation may be carried out through a single, 3 to 5 cm incision (uniportal), through which all the endoscopic instrumentation is inserted coaxially with the thoracoscope [47]. We are also now starting to adopt this approach, which provides the twofold advantage of a lesser invasiveness and the possibility of some manual palpation of the nodule(s) to be removed. The main pitfall of this technique, however, is that it can translate in more difficult and time-consuming surgical manipulations due to instrument conflict. Thus, in our opinion, uniportal NITOS operations should be undertaken only after having achieved adequate familiarity with equivalent procedures performed in anesthesized patients.

In our institution, we have performed more than 70 NITOS resections of SNPs, either with a standard or an uniportal approach. This policy allowed us to achieve a significant reduction in postoperative hospital stay (3 vs. 4 days) and in the average perioperative nursing workload (2.5 vs. 4 calls per patient/day) [41]. Also, we noted a trend to better postoperative oxygenation, and higher satisfaction score in patients treated this way. Further investigations, however, are needed to reinforce these preliminary findings, and to test the hypothesis of a reduced perioperative morbidity in the subgroup of high-risk patients.

Non-small cell lung cancer

In recent years, NITOS has emerged as an intriguing treatment option for the management of patients with stage I and II non-small

cell lung cancer. The most common indication is to perform wide wedge resections of early, peripherally located cancers in marginal surgical candidates, who are expected to benefit at most from an atraumatic surgical excision. The surgical technique is the same as for SNP removal of any origin. However, a particular attention should be paid to provide an adequately large tumor-free margin. Indeed, recent papers have shown that a >10-mm free-margin distance, or a distance which is equal to the tumor size, is associated with a significantly lower chance of local recurrences [49,50]. This goal is easily achieved in patients with peripheral nodule measuring less than 1 cm in diameter, in whom sublobar resections has been shown to provide non-inferior results compared to larger excisions [51]. However, in patients operated under spontaneous ventilation, obtaining an adequate tumor-free margin can be somewhat more difficult for lesions of larger size. In this regard, an useful trick is to grasp the nodule at its deeper pole by means of an endoscopic Satinsky forceps. A wider anterior videothoracoscopic access can also help this manouvre, as it allows the surgeon to detect the tumor boundaries by direct manual palpation. The endoscopic stapler can be then placed below the forceps, thus assuring an adequate amount of cut margin. We have treated in this way a small series of patients with an average Charlson comorbidity index of 5, achieving a 3-years survival rate of 72%. This figure seems not to be inferior to that reported with non-surgical ablative methods such as radiofrequency ablation and radiostereotaxis [41].

In general, wedge resection should be deemed as a less-than-ideal operation for NSCLC, and, at the present time, it should not replace anatomical excision in the vast majority of cases. However, some studies have suggested that, in peripherally-located tumors measuring 1 cm or less, wedge resections can be as effective as larger surgeries in terms of long-term survival chance [50-52]. It should be noted that these early cancers are expected to become increasingly detected thanks to the establishment of public health screening programs. For this reason, NITOS should be also viewed under the light of possible future development of tailored treatment protocols, which are expected to integrate tissue-sparing operations with molecular targeted therapies and monoclonal antibodies.

The use of NITOS to carry out videothoracoscopic anatomical lung resection for NSCLC is much more recent [43,53-55], even though occasional reports of major surgeries performed with regional anesthesia alone can be found in the historical surgical literature [56-58]. The National Taiwan University group must be credited for the introduction and development of this pioneering thoracic surgery field. The first report in this regard dates back to 2010, when Chen et al first reported on a preliminary series of 30 patients undergoing NITOS lobectomy [43]. Despite the limited study size, these authors found a clear trend toward a lower postoperative morbidity rate this group, when compared to matched patients receiving the same operations under general anesthesia. Since then, the number of performed procedures has remarkably increased. The last updates from the same group report more than 200 procedures to have been performed, even including 28 anatomical segmentectomies [43]. Despite the safety of merging videothoracoscopic approach with non-intubated anesthesia could be put into discussion, the authors have reported quite encouraging results in this regard. Indeed, the need of conversion to general anesthesia was well below 10%, and basically attributable to mediastinal movements, refractory hypoxia, and adhesions. More importantly, bleeding requiring urgent thoracotomy occurred in one patient only. These figures have been substantially reproduced by our group in a smaller series of 32 patients undergoing NITOS segmentectomies [58]. Oncology appropriateness seems also reliably achievable, as Cheng and coworkers reported no substantial difference as far as mediastinal lymph-node sampling was concerned [43]. Other limitations of NITOS to perform major lung resections are, however, to be discussed. Obviously, this surgical modality requires highest technical skills and familiarity with videothoracoscopic lung resections. It is also unclear whether to as the expected benefit in terms of postoperative morbidity can be reproduced in diverse patient's subcategories and risk classes. Finally, long-term results are not available yet, so that definitive conclusions in terms of overall survival and recurrence rates cannot be drawn at the present time.

Pulmonary metastasectomy

NITOS can be considered to perform videothoracoscopic removal of pulmonary metastases [41,59,60]. The ideal candidate is a patient with few (3 or less), easy-to-remove lung lesions, or a patient in whom excision of a single metastatic lesion is indicated for diagnostic purpose without the goal of complete resection. We have employed NITOS to treat a small series of patients with such features. When performing a matched comparison with patients undergoing standard videothoracoscopic metastasectomy, we found a significant reduction in global operative time (62 vs. 147 minutes, $p<0.001$, and in hospital stay (2.5 vs 4 days, $p=0.02$). Medium-term recurrences were similar between groups.

The main limitation of videothoracoscopy in the setting of pulmonary metastasecomy applies to NITOS as well, and consists in the difficulty to palpate the lung in search of radiologically-occult lesions, which may be found in more than 10% of patients. In the past, we used to employ a so-called substernal, hand-assisted thoracoscopic approach to overcome this problem. More recently, we tend to prefer a uniportal NITOS approach via a 5 cm anterior access. This approach allows an easy manual palpation of the targeted lung, which is also helped by partial inflation, with a quite reduced surgical traumatism. Uniportal NITOS may also replace a substernal approach to perform simultaneous bilateral operations, whenever the latter cannot be safely performed [61]. This may be the case of patients who had received previous median laparotomy to treat colorectal cancer, who are often referred to thoracic surgeons for pulmonary metastases. Patients with metastases from laryngeal cancer may also easily approach via NITOS, as permanent tracheostomy allows a rapid and safe control of the major airway should intubation become necessary.

Main contraindications to NITOS in this setting are redo metastasectomies, and previous ipsilateral radiotherapy, which could have been performed in breast cancer patients. One should also carefully investigate on the occurrence of pleural effusion which could have occurred at the time of the surgery for primary cancer removal. This complication, which may result in unmanageable pleural adhesions, may be frequently overlooked or completely forgotten by patients, especially if the perioperative recovery had been affected by more severe or troublesome conditions. Finally, the value of pulmonary metastasectomies in itself should be discussed, regardless of the adopted surgical modality. Indeed, despite many investigators have reported survival rates as high as 50%, the practice of metastasectomy is mostly based on observational studies or retrospective case series. We expect that the results of the dedicated randomized controlled trial currently underway in Europe will soon help shed new light on the management of this complex disease. The possible role of different anesthetic regimen on overall results of pulmonary metastasectomies, and their potential interaction with cancer progression, should also be addressed in future research.

Malignant pleural effusion

Patients planned for minimally-invasive management of malignant pleural effusion often present deteriorated clinical condition. Therefore, they are expected to benefit at most by avoidance of general anesthesia and OLV, which also appear to be disproportionate against the relatively simplicity of the procedure [45,61-63].

NITOS operation in these instances usually consists in aspiration of the effusion, pleural biopsy, and possibly pleurodesis in order to prevent recurrences. The patient can remain completely awake during the procedure, although *twilight* sedation may be needed in some instances. Different drug regimens can be used to this purpose, without any obvious advantage of one versus the others. The procedure can be usually performed with one small thoracoscopic access, with just local injection of anesthetic agents at the site of surgical opening. The opening of previously inserted chest drainage may be used as well, unless there is no sign of infection. Ten milliliters of a mixture containing 2% lidocaine and 7.5% ropivacaine is sufficient to provide a rapid and durable analgesic effect, so that it can cover the entire procedure. Additional injection(s) can be performed at the site(s) of pleural biopsy. A 20-mm flexible trocar should be preferred to allow insertion of a 30-degrees thoracoscope alongside with the other other operative instruments. Drainage of the pleural fluid is performed gradually, while the ability of the lung to expand is repeatedly checked by asking the patient to breathe deeply. Whenever lung expansion is deemed adequate, chemical pleurodesis can be indicated. To this purpose, we prefer use talc as the elective pleurodesic agent, due to its proven efficacy, and possible inhibition of tumor growth via an anti-angiogenetic effect [64]. Use of the large-particled (5-70 μm) talc powder has been shown to obviate the risk of serious postoperative complications such as acute-lung injury or pulmonary edema [62,65]. One should remind that talc insufflation within the pleural cavity may provoke pain in fully alert patients. Short-acting local anesthetics can be sprayed intrapleurally before proceeding with pleurodesis, and additional sedation may be given at this point.

Reported success rates for videothoracoscopic talc pleurodesis range from 84% to 95% [66-72]. These figures appear to be remarkably higher that those observed after bedside instillation of talc [68,70] or other agents [63,79]. We have evaluated comparatively the results obtained in a large series of patients with malignant pleural effusion, who were treated by either standard videothoracoscopy or NITOS. The latter resulted in a shorter duration of hospital stay ($p<0.014$), in a lesser perioperative complication rate (5.2% vs. 9%, $p=0.042$), and in reduced costs, with a mean saving of 3000 Eurodollars a patients [2]. Furthermore, NITOS seems to achieve better results in terms of early postoperative quality of life [71], and did not show inferior efficacy in achieving and effective pleurodesis. All these findings highlights that NITOS could be a reliable means to take the advantage of a videothoracoscopic procedure, while avoiding the risks related to general anesthesia in these fragile patients. Controversial results have been, however, reported by Debeljak et al. [72], who found a higher perioperative side-effect rate of videothoracoscopic pleurodesis under local anesthesia when compared with talc slurry (73% vs. 41%), and no superior efficacy.

When dealing with patients unfit for any surgical procedure, regardless of the type of aneshtesia, placement of an indwelling, tunneled intrapleural catether (PleurX®, Carefusion, USA) can be an option [73,74]. The latter device provides the advantages of a very short hospitalization, a simple insertion technique, and an easy home management. The PleurX catheter may be also be used at the end of a NITOS operation, whenever talc pleurodesis is not indicated because of unsatisfactory lung reexpansion. Potential pitfalls may include blockage, infection, and failure to achieve definitive pleural obliteration. Also, due to need for repeated home nursing assistance and outpatient visits, cost-effectiveness is reached only when restricting the use in patients with very short (<6 months) life-expectancy [74].

Mediastinal masses

Patients with huge mediastinal masses are more susceptible of serious anesthesia-related complications, including airway obstruction, bronchospasm, hypotension, and reflex arrhythmias [75,76]. In these patients, surgery can be required in order to expeditiously obtain a diagnostic sample and thus proceed with a life-saving treatment. Under these circumstances, NITOS operation may represent an useful option, even though its harm-to-benefit ratio versus non-surgical diagnostic methods should be carefully evaluated. The surgical route varies according to the localization of the lesion. Anterior mediastinal masses are well manageable by either non-intubated mediastinotomy [77,78] or videothoracoscopy [41]. The latter should be preferred whenever associated conditions possibly require videothoracoscopic management do exist [41]. These may include pleural or pericardial effusion, chylothorax, and associated pulmonary lesions of uncertain origin. The videothoracoscopic technique does not differ substantially from the same procedure performed under general anesthesia. A 45-degree flank position allows an easy videothoracoscopic approach to anterior mediastinum, and will facilitate switching to supine decubitus should emergent intubation become necessary. A single access at the 4th intercostal space is sufficient in many instances. One must remind that surgical manipulations of the inflamed mediastinal pleura can be painful, so that local anesthetics can be sprayed over this area before proceeding with biopsy. In our experience, we have treated this way a total of 23 patients with diverse mediastinal malignancies, reaching a 100% diagnostic yield with neither intra- or perioperative complication, nor need for switching to general anesthesia for any reason. All these patients had a various degree of superior vena cava compression or other associated signs including stridor and resting dyspnea. In 2 instances, NITOS allowed us to treat an associated, symptomatic pericardial effusion by means of a “window” technique.

One of the main concerns of NITOS in this setting, however, is the issue of airway control in case of unexpected surgical complications or sudden intraoperative asphyxia. The latter complication is significantly higher in patient with tracheal compression >50% (figure 2), and may be triggered by airway edema, surgical manipulations, and gravity compression from a gross paratracheal mass during lateral decubitus. In these instances, the surgical theater should be staffed and equipped to perform urgent rigid bronchoscopy, which may result a life-saving manouvre. Some authors even recommend being prepared to perform emergent extracorporeal circulation [76]. If the clinical situation portrays an elevated risk in this regard, a valid compromise solution could be to proceed with orotracheal intubation in the awake patient, and administer them sedatives while avoiding respiratory depression. The alpha-2 agonist dexmedetomidine can be particularly useful to this purpose, since it can provide light to deep sedation level without preventing spontaneous ventilation [79].

MACTS for thymoma and myasthenia gravis

Matsumoto has proposed NITOS thymectomy [80], performed via either median sternotomy or a videothoracoscopic technique, to treat myasthenia gravis, either associated or not with thymoma. The basic idea was to obviate the need of myorelaxants, which can be responsible for severe respiratory impariment in these patients. The operation was offered to patients with Myasthenia Gravis Foundation of America grade I-II patients, and having capsulated thymomas of less than 3 cm in size. The feasibility was excellent, and no relevant complication occurred in more than 30 treated patients.

Conclusions

In recent years, NITOS is being increasingly considered as an effective tool in the armamentarium of modern era thoracic surgeons. Even though there is no current level-A evidence to support or reject this practice, we are confident that future research, founded on a cooperative and constructive interaction between international centers, will soon provide a more robust knowledge to better define its advantages and limitations. Meanwhile, it would be desirable NITOS to be seen under a multidisciplinary light, rather than being merely considered as an ancillary surgical option. It is hopeful that thoracic surgeons will work in strict cooperation with anesthesiologists, oncologists, interventional radiologists, chest physicians, and specialized nurses to optimize at most the the decision-making process, as well as to design and conduct appropriate clinical trials on this topic. We also suggest that an appropriate training on NITOS should be awarded institutionally, and that the proficiency with this kind of surgery should be cerfied, rather than reported in a self-referentiality basis, to be listed as an extra credential when submitting application for surgical positions. For this reason, we have established an educational program, which has been approved by the research ethics board of our academic institution [2,3]. This program is founded on active participation of surgical residents and anesthesiologists to the NITOS sessions, with commitment to maintain the same team for at least 40 consecutive procedures a year. Lecture series, as well as educational tool as dry and wet labs and operating room simulations are also a part of our dedicated training. We are confident that such a policy will help increase at most the proficiency of our attending surgeons with NITOS procedures, and will ultimately help popularize the benefits of this practice amongst physicians and patients.

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Research Article Open Access

The Expression of the Thrombin Receptors PAR-3 and PAR-4 is Downregulated in Pancreatic Cancer Cell Lines

Claudia Rudroff[1*], Annette Richard[2], Sarah Hilswicht[3] and Edmund AM Neugebauer[2]

[1]*Department of General and Visceral Surgery, Evangelisches Krankenhaus Koeln-Weyertal, Cologne, Germany*

[2]*Institute for Research in Operative Medicine (IFOM), Faculty of Medicine, University of Witten/Herdecke, Cologne, Germany*

[3]*Department of General, Visceral and Transplantation Surgery, University Hospital Aachen, Pauwelsstr 30, 52074 Aachen, Germany*

[*]**Corresponding author:** Claudia Rudroff, Department of General and Visceral Surgery, Evangelisches Krankenhaus Koeln-Weyertal, Weyertal 76, 50931 Cologne, Germany, Tel: +49-221-479-2212; Fax: +49-221-479-2505; E-mail: clro@gmx.de

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Abstract:

Background: Patients with pancreatic cancer frequently suffer from thrombosis as a consequence of excess thrombin generation. In addition to its role in the plasmatic coagulation cascade, thrombin induces numerous cellular effects by activating a unique group of G-protein-coupled receptors on the cell membrane, the proteinase-activated receptors (PARs). At present, PAR-1, PAR-3 and PAR-4 are known to be activated by thrombin. We previously demonstrated a putative role for PAR-1 in pancreatic cancer progression, but little is known about the physiological and pathophysiological roles of PAR-3 and PAR-4. In the present study, we examined the expression patterns of PAR-3 and PAR-4 in pancreatic tissue and pancreatic cancer cells.

Methods: Tissue samples from three patients with pancreatic adenocarcinoma and six human pancreatic carcinoma cell lines were examined. Gene expression was analysed by RT-PCR and quantified by HPLC. Protein expression was determined by Western blot analysis. Data analysis was performed using ANOVA in SPSS.

Results and Conclusion: In contrast to PAR-1, both PAR-3 and PAR-4 were expressed in healthy pancreases but downregulated in pancreatic cancer. The contrasting expression patterns of PAR-3 and PAR-4 compared with PAR-1 indicate that the mechanism that regulates the cellular effects of thrombin on tumor progression remains to be fully elucidated.

Keywords: Gene Expression; Pancreatic Cancer; Protein Expression; Thrombin; Thrombin Receptors

Introduction

Thrombosis is a common complication of cancer; it is the second most common reason for death after the progression of the tumor [1,2]. Professor Armand Trousseau first described thrombophlebitis migrans as the first presenting sign of a gastrointestinal malignancy in 1864 [3,4]. Among gastrointestinal tumors, pancreatic cancer has the highest rate of thromboembolic complications [5]. Up to 40% of pancreatic cancer patients display symptoms of deep vein thrombosis (DVT) [6–9].

The activation of the coagulation cascade leads to the excess generation of the serine protease thrombin, its key enzyme. Thrombin plays a central role in activating several coagulation factors and splitting fibrinogen into the active product fibrin [10].

In addition to its diverse plasmatic actions, thrombin elicits numerous cellular responses, such as platelet aggregation, the secretion of cytokines from endothelial cells and the proliferation of fibroblasts and smooth muscle cells [11–13]. Thrombin has also been proposed to activate/aggravate the oncogenic potential of both normal and malignant cells [14–16]. The cellular effects of thrombin are mediated by a subgroup of G-protein receptors, the protease-activated receptors (PARs) [17,18]. PAR-1, the first identified protease-activated receptor [19,20], plays a crucial role in the activation of platelets and is thought to be the link between thrombin and the activation of the oncopathogenic potential in both benign and malignant cells via the aggravation of cell motility, tumor growth and angiogenesis [21–24].

We previously demonstrated poor PAR-1 expression in healthy pancreatic tissue and PAR-1 upregulation in pancreatic cancer tissue and pancreatic adenocarcinoma cell lines. The level of PAR-1 expression was inversely correlated with the grade of pancreatic cancer cells differentiation [25]. Furthermore, the activation of PAR-1 in pancreatic adenocarcinoma cell lines induced intracellular signalling, resulting in increased proliferation [26].

The recently cloned protease-activated receptors PAR-3 and PAR-4 also belong to the PAR family, but they have not been well characterised. Both PAR-3 and PAR-4 are specifically activated by thrombin [27–29], but their role in physiological and pathophysiological processes is not clearly understood.

The aim of this study was to determine the expression patterns of PAR-3 and PAR-4 in pancreatic cancer and to further characterise their putative role in thrombin-induced cancer progression.

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Methods and Materials

Tissue samples

Tissue samples from three patients with pancreatic adenocarcinoma were obtained from the tumor and healthy surrounding tissue and intraoperatively cryoconserved. Written informed consent was obtained from all the patients prior to surgery.

Cell culture and reagents

The human pancreatic carcinoma cell lines MIA PaCa-2 [30] (ATCC, Rockville, MD, USA); PATU 8902 and PATU 8988s [31,32], Capan-1 and Capan-2 [33,34], and DAN-G [35] (all DSMZ, Braunschweig, Germany) and Capan-1 (a gift from Professor Marc M. Mareel, University of Gent, Belgium) were cultivated in their respective media at 37°C in a humidified atmosphere with 5% CO_2 (see also Table 1). Human Umbilical Vein Endothelial Cells (HUVECs) (Boehringer Ingelheim, Heidelberg, Germany), which express PAR-4 were included as positive controls for PAR-4 expression. The medium and supplements were purchased from Biochrom Seromed (Berlin, Germany). Cell culture plastic ware was obtained from Nunc AS (Roskilden, Denmark).

RNA isolation and reverse transcription and polymerase chain reaction (RT-PCR)

Total RNA was isolated from pancreatic tissue samples, pancreatic cancer cell lines and HUVECs using a high-purity RNA tissue kit and a high-purity RNA isolation kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

For RT-PCR analysis, 250 to 500 ng of total RNA from each pancreatic adenocarcinoma cell line or tissue sample was used in SuperScript™ One-Step RT-PCR with Platinum® Taq (Invitrogen, Groningen, Netherlands) according to the manufacturer's instructions. Gene specific primer were designed using the web based primer blast software from ncbi (http://www.ncbi.nlm.nih.gov/tools/primer-blast/). The gene-specific primers for PAR-3 were as follows: sense 5'- CTG TTG CCC ACT TTT TGT CAG A –3' and antisense 5'- TGT TGC CCA CAC CAG TCC ACA –3'. The following PCR conditions were used to amplify PAR-3: 30 minutes reverse transcription at 53°C; 5 minutes initial denaturation at 94°C; 30 (tissue sample analysis) to 35 (cell lines) cycles of 20 seconds denaturation at 94°C, 30 seconds annealing at 60°C and 30 seconds primer extension at 72°C; and 10 minutes at 68°C for the final extension.

The gene-specific primers for PAR-4 were as follows: sense 5'- CAC CGG AGG TGG TGA TGA ACA GCA –3' and antisense 5'- GAA GGT CTG CCG CTG CAG TGT CA –3'. The PCR conditions were identical to those described for PAR-3 except that 38 cycles of annealing were performed at 66°C.

The β-actin gene served as an internal control. The gene-specific primers for β-actin were as follows: sense 5'-CCA AGG CCA AAC CGC GAG AAG ATG-3' and antisense 5'-GGT ACA TGG TGC CGC CAG AC-3'. The PCR conditions were as follows: 30 minutes of reverse transcription at 55°C; 3 minutes of initial denaturation at 94°C; 20 cycles of 20 seconds denaturation at 94°C, 30 seconds of annealing at 66°C and 30 seconds of primer extension at 72°C; and 10 minutes at 68°C for the final extension.

The PCR products were fractionated on agarose gels containing 0.5μg/μl ethidium bromide. The experiments were documented using a computerised gel documentation system (Gel-Pro Analyzer™, Media Cybernetics, USA).

The RT-PCR products were quantified by size-fractionation by anion-exchange High-Performance Liquid Chromatography (HPLC) on a Waters LCM1 plus system (Waters Cooperation, Milford, MA, USA). The peak areas corresponding to the RT-PCR product at 260 nm were integrated and normalised to the level of the β-actin message (Millenium Software, Waters Cooperation, Milford, MA, USA).

Cell lysates for protein analysis

Whole-cell lysates of the six pancreatic cancer cell lines (MIA PaCa-2, PATU 8902, PATU 8988s, Capan-1, Capan-2 and DAN-G) and HUVECs were prepared by lysing the cells directly in RIPA buffer (660–900 μl). The surfaces of Falcon flasks were scrapped with a rubber policeman, and the lysate was removed to a microcentrifuge tube, homogenised via passage through a 21-gauge needle and incubated for 60 minutes on ice. The samples were then centrifuged at 10000Xg for 10 minutes at 4°C to remove debris. The protein content was measured (DC Protein Assay, Bio-Rad, Germany) and the lysates were stored at -80°C until use.

Western blot analysis

Western blot analysis was performed using 35 μg of protein in each lane. All antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). For immunostaining, the membranes were incubated with the primary polyclonal anti-PAR-3 antibody (sc-5598; 1:1000; 4°C overnight) or the primary polyclonal anti-PAR-4 antibody (sc-1807; 1:1000; RT for 90 minutes), followed by incubation with the horseradish peroxidase-conjugated secondary antibody (sc-2371; 1:10,000; 45 minutes at RT). The immunoblotting results were visualised with a luminol-based chemiluminescence reagent and exposed to BIOMAX light-1 film (Kodak via Sigma Aldrich, Munich, Germany). For normalisation, each membrane was probed with an antibody against β-actin (sc-130657). The results were scanned and quantified.

Statistical analysis

All experiments were performed at least three times. Normalised PAR-3 RT-PCR products (μg/μl) and the results of the PAR-4 Western blot analysis (Integrated Optical Density, IOD) were used for statistical analysis with ANOVA in SPSS for Windows (IBM Germany, Ehningen, Germany). P-values ≥ 0.05 were considered statistically significant.

Results

Expression of PAR-3 mRNA

The expression of PAR-3 mRNA was determined in healthy pancreatic tissue and pancreatic adenocarcinoma samples. One pancreatic cancer cell line, PATU 8988s, was included in this experiment to compare the results from tissues and cell lines and rule out technical problems in RNA extraction from tissue samples.

High levels of PAR-3 were observed in healthy pancreatic tissue (1423 ± 669 μg/μl). However, in the corresponding pancreatic cancer tissue, the expression of PAR-3 (359 ± 13 μg/μl) was significantly

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down regulated. The expression levels of PAR-3 were even lower in the pancreatic cancer cell line PATU 8988s (23 ± 3 µg/µl) than in the pancreatic cancer tissue samples (Figure 1).

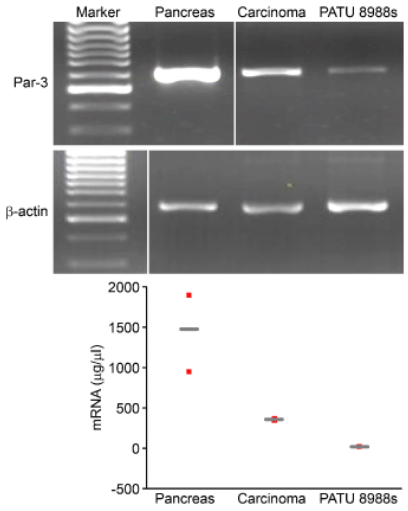

Figure 1: Expression of PAR-3 mRNA in tissue samples from a healthy pancreas (Lane 2), pancreatic cancer (Lane 3) and the pancreatic cancer cell line PATU 8988s (Lane 4), which was derived from a moderately differentiated pancreatic cancer specimen. The healthy pancreatic tissue showed strong PAR-3 expression. In pancreatic cancer tissue and in particular, the pancreatic cancer cell line, PAR-3 mRNA was significantly downregulated. The graph below shows the results of two independent experiments. The red dots represent the amounts measured by HPLC, and the grey bars indicate the mean.

The PAR-3 gene expression levels in the six pancreatic cancer cell lines with different grades of differentiation differed up to fivefold. The well-differentiated cell lines Capan-1 (1250 ± 145 µg/µl) and Capan-2 (1120 ± 120 µg/µl) exhibited comparatively high levels of PAR-3 expression. The moderately differentiated cell lines PATU 8902 (785 ± 5 µg/µl), DAN-G (756 ± 66 µg/µl), and PATU 8988s (706 ± 45 µg/µl) exhibited markedly lower PAR-3 gene expression. The differences between the well-differentiated cell lines (Capan-1 and Capan-2) and the moderately differentiated cell lines (PATU 8902, PATU 8988s and DAN-G) were statistically significant ($p=0.005$ to $p<0.001$). Very low levels of PAR-3 expression were observed in MIA PaCa-2 (232 ± 11 µg/µl), a cell line with poor differentiation and high malignant potential. This result was statistically significant compared to both Capan-1 and Capan-2, with $p<0.001$ (Figure 2).

PAR-3 protein expression

The protein expression of PAR-3 also correlated with the differentiation level of the pancreatic cancer cell lines. In the well-differentiated cell lines Capan-1 and Capan-2 and in DAN-G, PAR-3 protein expression was observed, but no difference in expression between these cell lines was observed.

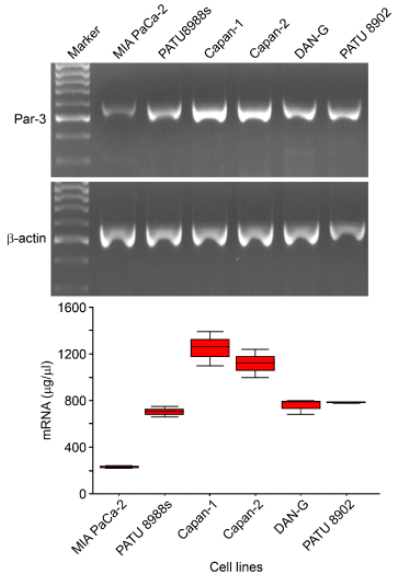

Figure 2: PAR-3 gene expression analysed by RT-PCR in six pancreatic cancer cell lines with varying grades of differentiation. The agarose gel shows different levels of PAR-3 (640 bp) in the upper image and β-actin expression as an internal control (585 bp) in the lower image. Both products were fractionated in ethidium bromide-stained 2% agarose gel using horizontal gel electrophoresis. The graph shows the amounts of mRNA in µg/µl from a set of four independent experiments as box plots. The differences in PAR-3 gene expression levels between the well-differentiated pancreatic cancer cell lines Capan-1 and Capan-2, the moderately differentiated cell lines PATU 8988s, DAN-G, and PATU 8902 and the poorly differentiated pancreatic cancer cell line MIA PaCa-2 were statistically significant.

No PAR-3 protein expression was detected in the moderately differentiated cell lines PATU 8988s and PATU 8902 and the poorly differentiated cell line MIA PaCa-2 (Figure 3).

Expression of PAR-4 mRNA

High mRNA expression levels of the thrombin receptor PAR-4 were observed in healthy pancreatic tissue. However, PAR-4 mRNA was downregulated in the corresponding pancreatic cancer tissue to below the detectable level (Figure 4). Accordingly, PAR-4 gene expression was below the detectable level in all RNA samples from the tested pancreatic adenocarcinoma cell lines. Consequently, no statistical analysis could be performed. As a control, PAR-4 mRNA was detected in endothelial cells (HUVECs), ruling out primer dysfunction or technical problems (Figure 5).

PAR-4 protein expression

Weak PAR-4 protein expression was detected in all pancreatic adenocarcinoma cell lines tested. The expression levels of PAR-4 did not differ between the different cell lines. In the endothelial cells (HUVECs) used as a control, a strong PAR-4 protein signal was observed (Figure 6).

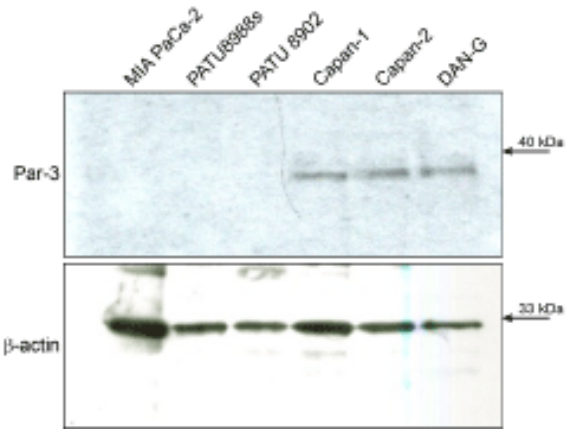

Figure 3: Representative Western blot analysis of PAR-3 protein expression in whole cell lysates of six different pancreatic cancer cell lines (MIA PaCa-2, PATU 8988s, PATU 8902, Capan-1, Capan-2 and DAN-G). The upper image shows that PAR-3 is only expressed in the pancreatic cancer cell lines Capan-1, Capan-2, and DAN-G. The PAR-3 protein has a size of approximately 40 kDA. The lower image shows the membrane reprobed for β-actin, which was used as an internal control, at 33 kDA. Although the β-actin expression varies between the cell lines, all cell lines show expression, thereby ruling out technical faults.

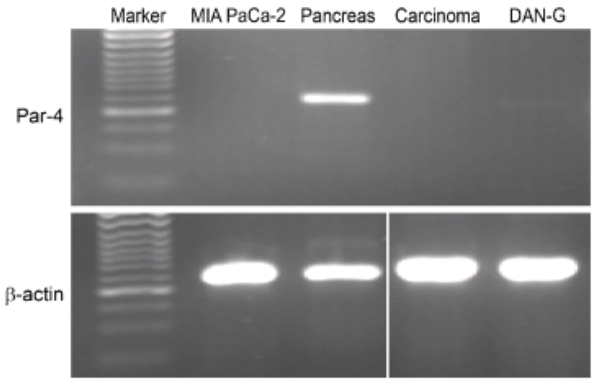

Figure 4: Representative RT-PCR analysis of the expression of PAR-4 mRNA in tissue samples from a normal pancreas (Lane 3), pancreatic cancer (Lane 4) and the two pancreatic cancer cell lines MIA PaCa-2 (Lane 2) and DAN-G (Lane 5). Strong PAR-4 expression was observed in healthy pancreatic tissue. PAR-4 mRNA could not be amplified from the pancreatic cancer tissue and the pancreatic adenocarcinoma cell lines.

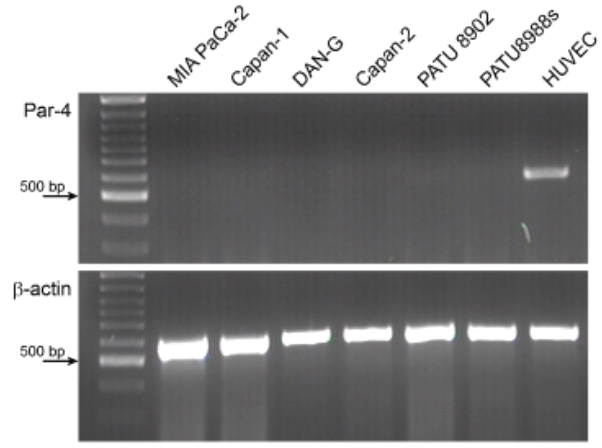

Figure 5: Representative RT-PCR analysis of PAR-4 expression using total RNA from six different pancreatic cancer cell lines (Lanes 2-7) and HUVECs (Lane 8). The upper image shows the PAR-4 PCR product, which has a size of 581 bp. The lower image shows the PCR products for β-actin, a housekeeping gene that served as an internal control, at 598 bp. Lane 1 in both pictures shows the molecular weight marker (100 bp PLUS, PeqLab, Erlangen, Germany); the band corresponding to 500 bp is indicated by the arrow.

Discussion

Patients with pancreatic carcinoma frequently suffer from thrombosis as a result of an excessively activated coagulation cascade and thrombin generation [6,9,10,36]. The thrombin receptor PAR-1 plays a role in the activation of platelets and is thought to be the link between thrombin and the activation of oncopathogenic potential in both benign and malignant cells [22-24]. The effects of thrombin on pancreatic cancer progression and the associated underlying mechanisms by which the diverse thrombin receptors, particularly PARs, are orchestrated are still not completely understood.

In this study, we investigated the expression of the recently cloned receptors PAR-3 and PAR-4 in pancreatic cancer tissue and cell lines for the first time.

Gene expression of PAR-3 was detected in healthy pancreatic tissue. In contrast with its high expression in healthy tissue, the level of PAR-3 mRNA was significantly decreased in pancreatic cancer tissue and pancreatic cancer cell lines.

Furthermore, the level of PAR-3 gene expression in six pancreatic cancer cell lines correlated with the degree of differentiation of the cell lines. PAR-3 gene expression was lower in the moderately differentiated pancreatic cancer cell lines (PATU 8988s, DAN-G, and PATU 8902) compared with the well-differentiated pancreatic cancer cell lines (Capan-1 and Capan-2). The downregulation of PAR-3 mRNA expression was most evident in the poorly differentiated pancreatic cancer cell line MIA PaCa-2. PAR-3 expression was up to fivefold lower in MIA PaCa-2 than in the better differentiated pancreatic cancer cell lines.

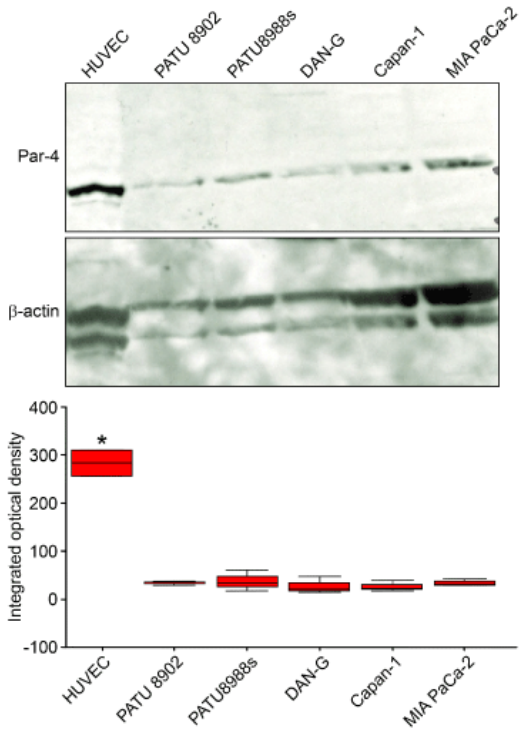

Figure 6: Representative Western blot analysis of PAR-4 protein expression using whole cell lysates derived from five pancreatic cancer cell lines (PATU 8902, PATU 8988s, DAN-G, Capan-1 and MIA PaCa-2) and HUVECs (Lane 1). The upper image shows PAR-4, which has a size of approximately 40 kDA. PAR-4 expression was strongest in HUVECs. The expression of PAR-4 did not vary significantly between the pancreatic cancer cell lines. The lower image shows the reprobed membrane. In the graph below, the box plots represent the integrated optical density from three independent experiments. The graph illustrates the significant difference in PAR-4 expression in HUVECs and the pancreatic cancer cell lines ($p<0.005$ = *).

The analysis of PAR-3 protein expression in the pancreatic cancer cell lines revealed specific variations. As expected, protein expression was detected in the well-differentiated cell lines Capan-1 and Capan-2. However, similar protein expression was confirmed for the moderately differentiated cell line DAN-G, whereas none of the other cell lines exhibited protein expression of PAR-3.

The mechanism of PAR-3 activation remains unknown. PAR-3 was first described in PAR-1-deficient mice, the platelets of which are fully responsive to thrombin [37]. Although the PAR-3 consensus sequence contains a putative thrombin cleavage site, no synthetic peptide is able to mimic receptor activation and function [38]. Interestingly, the tethered ligand peptide for PAR-3 interacts with PAR-1 and PAR-2 in Jurkat cells [39]. In mice, PAR-3 functions as a co-factor for PAR-4 in platelet activation [40].

In human endothelial cells, PAR-3 regulates PAR-1 signalling by receptor dimerisation, resulting in increased endothelial permeability [41]. In human rhabdomyosarcoma, PAR-3 inhibits tumor cell proliferation and growth [42].

Because PAR-3 is an apparent factor in the inhibition of tumor proliferation, the observed downregulation of PAR-3 emphasises the PAR-3's putative role in controlling tumor growth and malignant potential. Because of receptor heterodimerisation, the downregulation of PAR-3 further increases the oncogenic potential of PAR-1 in pancreatic cancer.

The mRNA of the thrombin receptor PAR-4 was expressed in healthy pancreatic tissue. In the corresponding tissue from pancreatic cancer, no PAR-4 mRNA was detectable. Accordingly, PAR-4 mRNA expression was below detectable levels in all of the pancreatic cancer cell lines.

Contrary to the gene expression results, PAR-4 protein expression was detectable in all whole-cell lysates of the pancreatic cancer cell lines, although the detection levels were low. Post-transcriptional and post-translational modifications, a well-known phenomenon for G protein-coupled receptors, may explain the discrepancy between the mRNA and protein results in our experiments [43].

Both PAR-4 and PAR-1 are activated by thrombin via the cleavage of a specific extracellular domain. Receptor activation and function can be mimicked by synthetic peptides representing the tethered ligand sequence. Interestingly, PAR-4 requires much higher concentrations of thrombin (1 U/ml or greater) than PAR-1 for activation and might serve as a modulator of the cellular dose-response to thrombin [28]. Thus, it has been hypothesised that PAR-4 might induce conflicting effects if it serves as a natural shut-off for PAR-1. This relationship has been confirmed for the effect of PAR-1 (contraction) and PAR-4 (relaxation) on the muscularis mucosae in the rat oesophagus [44].

If PAR-4 also serves as a shut-off for PAR-1 at high thrombin concentrations in a cancer setting, our results indicate that the downregulation of PAR-4 together with the upregulation of PAR-1 in pancreatic cancer strengthens the malignant potential of thrombin because the regulatory function of PAR-4 is missing.

Our results are supported by the reported PAR-4 expression in human lung adenocarcinoma. PAR-4 expression is decreased in lung adenocarcinoma and is associated with poor differentiation and metastasis [45].

In a murine model using a melanoma cell line, PAR 4 -/- mice displayed a significantly lower tumor burden and less distant metastasis [21], but this model does not address the role of PARs in the tumor cells themselves.

Our results reveal a contradictory regulatory mechanism for the expression of the thrombin receptors PAR-3 and PAR-4 compared with PAR-1 in pancreatic cancer tissue and pancreatic adenocarcinoma cell lines. In contrast to PAR-3 and PAR-4, the thrombin receptor PAR-1 is not expressed in healthy pancreatic tissue. However, PAR-1 is upregulated during malignant transformation, and the level of PAR-1 expression correlates with the grade of malignancy [25]. By contrast, PAR-3 and PAR-4 are downregulated during tumorigenesis and the de-differentiation of pancreatic cancer.

The downregulation of both PAR-3 and PAR-4 in pancreatic cancer compared with healthy pancreatic tissue further supports a role of both receptors in cancer progression.

Furthermore, if PAR-4 act as a shut-off for PAR-1 and PAR-3 also serves as an important receptor for heterodimerisation in PAR-1 signalling in the pancreas, our experiments would imply that

pancreatic cancer progression is governed by both the upregulation of PAR-1 and the downregulation of PAR-3 and PAR-4.

Conclusion

We demonstrated that the thrombin receptors PAR-3 and PAR-4 are both present in healthy pancreatic tissue. Our results show that both receptors are significantly downregulated in pancreatic cancer tissue and pancreatic cancer cell lines. The regulation of PAR-3 and PAR-4 contrasts with that of the thrombin receptor PAR-1, which is merely detectable in the healthy pancreas but is significantly upregulated in pancreatic cancer tissue and pancreatic cancer cell lines.

Although little is known about the role of PAR-3 and PAR-4 in pathophysiological mechanisms, our results imply their involvement in the progression of pancreatic cancer. Given the key role of thrombin in the context of tumor progression, the role of the thrombin receptors PAR-3 and PAR-4 in pancreatic cancer merits further study.

Acknowledgement

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Macrophage Quantification in Different Breast Tumor Compartments

Anca Haisan[1], **T Petreus**[2], **Daniela Jitaru**[3], **M Danciu**[4] **and E Carasevici**[3]

[1]*Emergency Medicine Department,"Gr.T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

[2]*Department of Cell Biology, "Gr.T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

[3]*Laboratory of Molecular Biology, Regional Institute of Oncology, Iaşi, Romania*

[4]*Pathology Department "Gr.T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

[*]**Correspondence author**: Anca Haisan, MD,Emergency Medicine Department, "St. Spiridon" Hospital, Iaşi, Romania, Independenţei Street, No 1, 700111, Iaşi, Romania, Tel: +40 (0) 232 21 77 81; Fax: +40 (0) 232 21 77 81; E-mail: anca.haisan@gmail.com

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Abstract

Background and Aim: Breast cancer shows poor prognosis when tied with chronic inflammation mediated by tumor associated macrophages (TAM). However, TAM's multiple role, localization and prognosis are still debatable. Our study aims to quantify macrophage area and compare defined tumor morphological compartments: tumor associated stroma (TAS), tumor parenchyma and invasive front.

Material and Methods: Automated digital macrophage area quantification was standardized using a tissue cytometry system (TissueFAXS) on slides originated from 50 patients with invasive breast carcinoma. Macrophages were stained using immunohistochemistry with anti-CD68 marker. The three tumor compartments were manually delineated on the digital slides.

Results: Macrophage area was 3 times higher in lymph node-negative metastasis patients (pN0 group) when compared to lymph node-positive group in tumor and invasive front compartments. Highly significant strong correlations were found between the three compartments only in pN0 group (i.e. R >0.90, P<0.001) while pN+ group showed weak ones suggesting various macrophage roles. CONCLUSION: Compartment-specific automatic quantification of macrophages in invasive breast carcinoma provides more insight on their role in tumor outcome. The new method applied in our study shows compartments' variability of local macrophage density and highlights behavior differentiated by the presence of metastasis.

Keywords: Breast Cancer; Tumor Compartments; Macrophage Area; Cd68; Invasive Front; Computer Image Analysis

Introduction

Many malignancies, including breast cancer, show poor prognosis when associated with chronic inflammation, usually mediated by special monocyte-derived cells – the tumor associated macrophages (TAM) [1-3]. In solid tumors, macrophages represent a constant presence. Due to their dual behavior, pro and anti-inflammatory [4-6], the TAM effects on tumor site depend on the macrophage secreted molecules [7-9] and also on their surface markers and density. CD68 TAMs were subject for wide investigations and reviews, mainly in breast cancer [10-14]. Mantovani et al demonstrated that TAMs are usually of M2 type, with enhanced tumor inducing functions, cell survival supportive effects and antiapoptotic [3,15-17]. CD68 TAMs distribution in breast cancers was investigated by various methods, mainly immunohistochemistry on tissue microarrays blocks [14,18,19]. Evaluation methods for CD68 TAMS in various tumor areas or according to lymph node involvement are also fluctuating, from microscopic observations to molecular biology methods [20-22]. Data interpretation regarding CD68 TAMs presence in breast tumors shows inconsistent correlations between TAMs localization and prognosis. Thus, the aim of this study is to perform a computer assisted measurement of relative stained area index in three defined tumor compartments - tumor associated stroma, tumor parenchyma and invasive front – in order to show differences in local density for CD68 tumor associated macrophages.

Materials and Methods

Patients and tissues

Our cohort was comprised of 50 samples of invasive breast carcinoma patients between 37 and 70 years old (mean age 57), of No Special Type (NST). Patients were without any adjuvant hormonal or chemotherapy previous to the surgical resection. We have obtained additional information for each patient, as medical pathological records; each tumor was classified according to its' pathological pattern.

Immunhistochemistry

All tumors were formalin fixed. Sections 5 µm thick from paraffin embedded tumor blocks were mounted on adhesive slides for both test samples and negative controls. Sections were deparaffinated in xylene baths and rehydrated in graded alcohols to water (90%, 70%, 50% and 30%) 5 minutes each bath. For antigen retrieval we used HIER method with a steamer (98°C for 30 minutes), in high pH Dako retrieval solution; after 30 minutes, slides were cooled at room temperature in retrieval solution, then washed in Tris-buffered saline (TBS) solution 3 times for 5 minutes each. Endogenous peroxidase activity was

quenched by 0.3 H2O2 at room temperature for 10 minutes. After TBS washing again (3 times for 3 minutes each), blocking solution was used (Protein Block Serum-Free, Ready to use, Dako). The slides were then washed with TBS 3 times of 3 minutes each. Test lot was incubated over night at 4 Celsius degrees after applying primary antibody mouse monoclonal ab955 [KP1] anti CD68 Abcam, at a 1:300 dilution. The negative control lot was incubated in the same manner but using monoclonal mouse IgG1 antibody instead of the primary antibody. Second day we applied on both lots biotinilated link and detection complex, LSAB–kit Dako. Developing reaction was made with DAB chromogen and after that, counterstained with Mayer's haematoxylin, fixed in tap water, dehydrated in alcohol and xylene clarified, mounted and cover slipped.

Scanning procedure

Digitization and analysis were performed with TissueFAXS 3.5 (TissueGnosticsGmbh, Vienna, Austria) which included the scanning system in addition to the cytometry analysis software (TissueQuest and HistoQuest). The scanner consisted of a Zeiss Imager Z2 microscope, a 3 Megapixel colour camera Pixelink PL-623 CF and a motorized stage from Maerzhauser with 8-slide insert for the batch scanning mode. The white light lamp was a VISLED based on LED technology providing a stable intensity during the study. The analysis computer was a HP Z400 equipped with an Intel Xeon W3565 processor at 3.2 GHz running Windows7 (64bit).

A 10x objective was used for the image acquisition. Established microscope parameters were checked before scanning, as well as the Koehler illumination procedures described in Zeiss Imager manuals. The sensor of the camera was aligned to the axis of the stage so that the angle between them was less than 0.01 degrees, thus minimizing mosaic image alignment shifts. TissueFAXS 3.5 saved the images in JPEG format with a 95% quality index. The virtual slides were merged using a 15% image overlap between neighboring images. Shading compensation was performed using a shading correction image acquired with same camera settings. Exposure time of the camera was set such that pixels in white background had a value 230-240 on all red, green and blue channels. White balance was realized only once using the automatic feature in an image without tissue. Linear behavior of the sensor was ensured by disabling gamma adjustments. Lamp and camera parameters were saved in a TissueFAXS intensity profile, then reused for all slides of the study, such that images were acquired with a consistent comparable quality. The digital slides were 58 GB in size on a NTFS formatted hard disk; Total scanned area over the entire set of 50 patients was 46862 mm^2.

Definition of regions of interest

Visual analysis of the digital slides was performed in an initial phase using contextual assessment from a pathological point of view. Locations of tumor area (parenchyma) (T), tumor associated stroma (TAS) and invasive front (IF) were identified in each section. The tumor area having an irregular shape, consisted in ducts, nests and cords of tumor cells. We considered the invasive front of the tumor the interface between the adjacent breast tissue and the periphery of tumor. The pattern of the tumor growth was often infiltrating and widely dissecting the normal breast tissue, without clear boundaries between host tissues and tumor. Tumor budding was found in the invasive front, exhibiting small aggregates or isolated tumor cells. Tumor associated stroma (TAS) was outlined as the fibro-vascular tissue (microenvironment) surrounding or including the malignant cells. Studies of the desmoplastic reaction found that TAS is a useful histological prognostic parameter in breast cancer [27]. Using Ueno's criteria [27] for classification of fibrotic cancer stroma we classified our cases as having: mature, intermediate or immature fibrotic stroma.

Several sites (n=1-3) were chosen for analysis using Standard Regions of Interest (ROI) tool, each site selected with a predefined disk shape of 1 mm diameter. Contours of each area were highlighted in green, blue or red, for stroma (green), tumor (blue) or invasive front (red), respectively. Colored highlighting increased speed of secondary opinion analysis and during post-analysis checks since the areas were easily observed. Selections of ROIs were made avoiding folded tissue, areas with mechanical disrupted morphology generated by cutting, air bubbles within mounting medium or major staining artifacts.

ROIs were defined in two phases. First, 2 medical doctors independently highlighted the areas for analysis. A second review phase was performed by the entire team for reaching final agreement on ROI sites in all samples (Figure 1, 2 and 3).

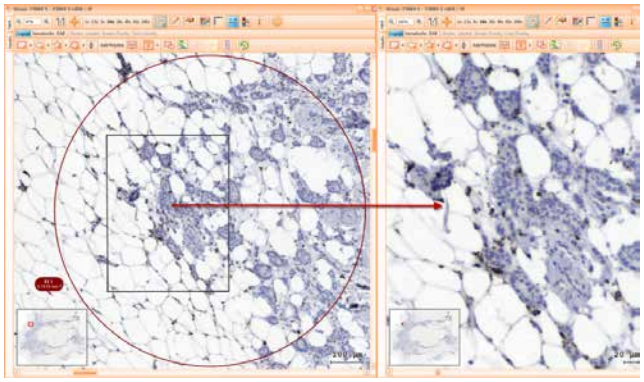

Figure 1: Selection of invasive front stained with CD68; detailed view on the right side.

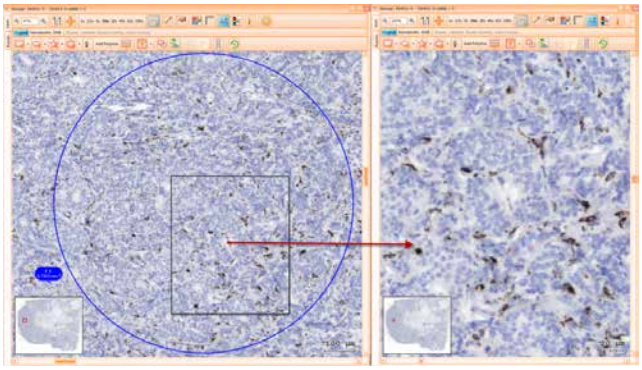

Figure 2: Selection of tumor stained with CD68; detailed view on the right side.

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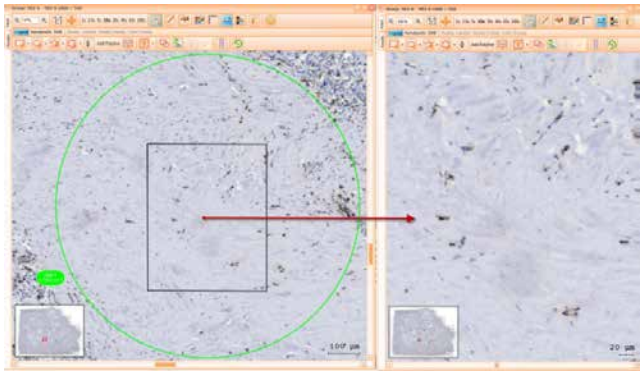

Figure 3: Selection of tumor associated stroma stained with CD68; detailed view on the right side.

Measurement procedure

HistoQuest 3.5 software was used for quantitation. HistoQuest analysis projects imported TissueFAXS digital slides, considering available shading correction and image tile overlapping information. The software unmixes the color RGB image into marker-specific optical density images with an algorithm for colour separation selected using Single Reference Shade module. Thus it separates Hematoxylin and CD68-DAB into their Optical Density (OD) counterparts. The training procedure is done by pointing with the mouse pixels for each of the two stains. In the CD68-DAB optical density images, positive areas were measured by manual thresholding and quantifying Stained-Area (SA) using Total Area Measurement option. The threshold was found after an iterative search in several samples by looking at the resulting overlays of detected contours on the original images. The software allows interactive threshold definition. Best settings found on representative small test regions were saved in a "marker profile" of HistoQuest and then applied in all analysis projects of the study using the "batch analysis" module, for unattended automatic computation.

Validation of macrophage area detection

After quantification, a visual validation of proper SA identification was done on all digital slides. Each project was reopened for assessment of overlays of macrophage contours on the colour images. "Add event" from "Manual Correction Module" was used to indicate areas which were too weak for automatic detection. Identified areas which were not macrophages, such as staining artifacts or high background, were deleted from analysis using "Delete Events". Only 5 digital samples needed manual corrections of the automatic stained area identification.

Extraction of quantitative data

Validated measurement results were extracted from the analysis projects using Batch Export module in a single Excel file: total Analyzed Area (AA) and total Stained Area (SA) of each domain of each patient. Derived results were calculated directly in Excel: the Relative Stained Area (RSA) for each domain (RSA percent = 100 x SA / AA). SPSS 19 software was used for statistical analysis.

Results

Macrophage quantitation

Macrophage stained area was measured in each compartment of TAS, T and IF, for patients in group pN_0 (no metastasis), for those in pN positive (node metastasis present) as well as for all patients (Table 1).

Table I: Average values for TAS, T and IF compartments in N0 group, N+ group and all patients respectively. TAS Tumor Associated Stroma; T Tumor aria (parenchyma); IF Invasive Front.

Group	Average Relative Stained Area (RSA)		
	TAS - RSA	T - RSA	IF - RSA
N0	0.46	0.63	0.58
N+	1.06	1.79	1.5
Overall	0.97	1.62	1.37

Patients in pN0 showed values of 0.46, 0.63 and 0.58 for TAS, T and IF respectively. Patients in group pN positive revealed average compartment measurements of 1.06, 1.79 and 1.5 respectively, values 2-3 times higher than those in N_0 group. When looking at the entire population of patients, mean values were calculated as 0.97, 1.62 and 1.37. All three groups revealed the same sorted trend of higher CD68 areas in tumor, followed by lower values in invasive front; whereas tumor associated stroma had lowest values of all three compartments. Values from Table I were displayed graphically in Figure 4.

Statistical analysis

Pearson correlations between all possible pairs of compartments were calculated for patients without node metastasis (Table II).

Strong correlations were found in all pairs (0.908, 0.922 and 0.749 respectively), with a highly significant p values (less than 0.05 for all cases).

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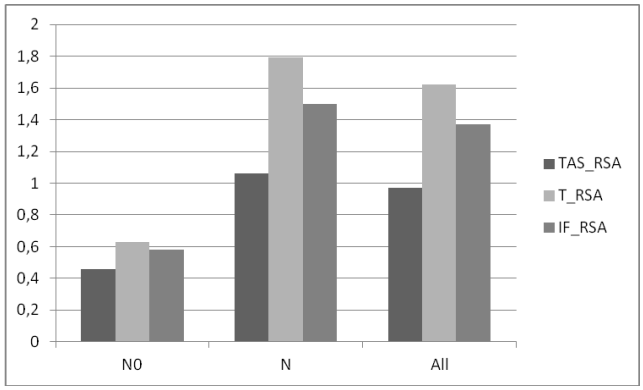

Figure 4: Graph showing average values of CD68-RSA measurements for N0, N+ and entire population in all three compartments (TAS, T and IF) TAS Tumor Associated Stroma; T Tumor aria (parenchyma); IF Invasive Front; RSA Relative Stained Area.

For patients with node metastasis, a relatively weak correlation was found only in the "TAS & T" pair, but with a highly significant p value (less than 0.001) (Table 3).

Table II: Statistical analysis for all compartment pairs for patients without node metastasis. TAS Tumor Associated Stroma; T Tumor aria (parenchyma); IF Invasive Front.

Compartment pairs	n	Correlations		Paired Differences
		Pearson correlation (R)	P	P
TAS & T pair	10	0.908	< 0.001	0.108
TAS & IF pair	10	0.922	< 0.001	0.204
T & IF pair	10	0.749	0.013	0.560

Statistical assessment of entire patient cohort showed a significant (P less than 0.001) but weak correlation (P = 0.677) only in the "TAS & T" pair (Table 4).

This leads to the idea that macrophages in stroma may be functionally linked to those in the tumor area, while the macrophages in the invasive front express a different functional behavior than the other two compartments.

Table III: Statistical analysis for all compartment pairs for patients with node metastasis. TAS Tumor Associated Stroma; T Tumor aria (parenchyma); IF Invasive Front.

Compartment pairs	n	Correlations		Paired Differences
		Pearson correlation (R)	P	P
TAS & T pair	40	0.620	<0.001	0.061
TAS & IF pair	40	0.235	0.144	0.459
T & IF pair	40	0.498	0.001	0.391

Table IV: Statistical analysis for all compartment pairs for all patients. TAS Tumor Associated Stroma; T Tumor aria (parenchyma); IF Invasive Front.

Compartment pairs	n	Correlations		Paired Differences
		Pearson correlation (R)	P	P
TAS & T pair	50	0.677	<0.001	0.020
TAS & IF pair	50	0.368	0.009	0.341
T & IF pair	50	0.559	<0.001	0.299

Discussions

Regarding human breast cancers, most of the previously published studies [19,23,24] demonstrate the main infiltrative tumor associated macrophages (TAM) role in tumor evolution and patient prognosis. Macrophage precursors are being recruited to and activated in the tumor site in breast cancer, as demonstrated by some exhaustive reviews [19,23,24]. Monocytes are being attracted to the tumor site by various chemokines as IL10 and TGFβ [19]. Previous findings on CD68 macrophage density in human breast tumor areas are contradictory and probably depend on the inconstant assessment methods or on various markers used. Leek et al [25] or Lee et al. [26] reported a diffuse infiltration pattern for TAM with no detail regarding their distribution in different tumor areas. Various statistical methods, as multivariate and univariate analysis, were applied for defining a connection between CD68 macrophages infiltration and prognosis but the results were contradictory [2,19].

The present study is assessing TAM distribution by an original method of quantitative relative stained area measurement, dividing the tumor area in three regions of interest: tumor associated stroma, tumor parenchyma and invasive front. Furthermore, comparisons

were performed among metastatic (pN > 0) and non-metastatic (pN0) breast tumors. Even if our study was performed on only 50 cases compared to 1322 [19] or 101 [2] and a panmarker was used to stain macrophages, the information obtained are consistent with some authors [2,14] and contradicting with others [19]. Medrek [14] observed in a study on 144 cases that CD68 macrophage infiltration was present in 17% cases in the tumor parenchima and only 6% in tumor stroma.

Our study introduces standardized scanning procedures as well as contextual compartment specific analysis using predefined rules and visual validation methods. Measurements in defined tumor associated stroma, tumor parenchyma, invasive front showed variations in local CD68 macrophage density. Not only is the cell density correlated with tumor degree and partially with the prognosis but apparently also macrophage distribution in tumor areas. Our results are consistent in metastatic and non-metastatic groups and show higher CD68 TAM density in tumor site over the invasive front and tumor stroma. At the same time, in metastatic (N) group we have observed a three time increase of CD68 macrophages in tumor areas compared to the non-metastatic (N0) group, probably due to tumor necrosis and local hypoxia. The same pattern was found in the invasive front while in the tumor stroma, the increase of CD68 macrophage density was only two times in N compared to N0. Thus, regarding consistent CD68 macrophages density variations in different tumor areas, we underline the importance of assessing TAMs distribution in metastatic and non-metastatic breast cancers.

High correlation between all three compartments found in N0 group may suggest that the macrophage play the same functional role. In the group of node metastatic patients, the fact that the invasive front had a very weak correlation with the other two compartments may indicate that many macrophages could play a different role in tumor and stroma, as opposed to invasive front, which is associated with epithelial-mesenchymal transition. Further studies which use simultaneously additional markers such as CD163 (M2-proangiogenic macrophages) and CD105 (tumor angiogenesis) seem to be necessary and could reveal more insight on the role of macrophages in breast invasive carcinoma.

Conclusions

Traceability and observer independence were improved by whole slide scanning and virtual annotation of the tumor compartments. The proposed method of relative stained area index for each of the tumor domains (tumor associated stroma, tumor parenchyma, invasive front) showed relevant differences, with higher values for tumor and invasive front, in contrast with lower values found in tumor associated stroma. When looking at groups of patients based on presence of metastasis, lymph node-negative patients revealed 3 times less CD68 stained area in both tumor and invasive front compartments. In N0 group, the high correlation between all three compartments may suggest that the macrophage play the same functional role. In contrast, in the group of node metastatic patients, the invasive front had a very weak correlation with the other two compartments indicating that macrophages could play a different role in tumor and stroma, as opposed to invasive front. The proposed scoring procedure provides a more precise measurement tool with a significant impact for patient management and eventually treatment individualization, once macrophage role is better understood. Pathologist experience in delineating tumor compartments according to morphological heterogeneity combined with our method of visually validated quantification reveal new perspectives on macrophage role in invasive breast carcinoma, for clinical diagnosis.

Conflict of Interests

Authors have no conflict of interests to declare.

Aknowledgements

The first author is Ph.D. student at "Gr.T. Popa" University of Medicine and Pharmacy, Iaşi, Romania. This paper is the result of the work undertaken during the doctoral internship.

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Research Article Open Access

Impact of Chronic Pancreatitis on Pancreatic Resections for Malignancy

Jill K Onesti[1,2*], **G Paul Wright**[1,2], **Payal P Attawala**[2], **Deepali H Jain**[1,2], **Arida Siripong**[1] **and Mathew H Chung**[1,2,3]

[1]*M.D, GRMEP/MSU General Surgery Residency, Grand Rapids, MI, USA*

[2]*Michigan State University College of Human Medicine, Grand Rapids, MI, USA*

[3]*Spectrum Health Medical Group, Grand Rapids, MI, USA*

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[*]**Corresponding author:** Jill K Onesti, M.D. 221 Michigan St NE, Grand Rapids, MI 49503, USA Tel: 616.391.1691, Fax: 616.391.8611, E- mail: **jill.onesti@grmep.com**

Abstract

Background: Chronic pancreatitis has been shown to have potential benefit in pancreatic resections by reducing postoperative pancreatic fistula. We sought to investigate the impact of chronic pancreatitis on oncologic surgical outcomes.

Materials and Methods: Consecutive partial pancreatectomies performed for malignant disease from 2005-2011 were reviewed. Patients were divided for analysis based on the presence of chronic pancreatitis. The primary outcome measures were need for intraoperative re-excision of margins and final margin status. Secondary outcome measures included pancreatic fistula rate and overall morbidity which were graded in standardized fashion. Significance was assessed for $p<0.05$.

Results: One hundred fifty-four patients met criteria for study, 48 of which had chronic pancreatitis. Demographics, co-morbidities, diagnoses, and surgical technique were equivalent between groups. Though there was a trend towards increased re-excision of margins in the chronic pancreatitis group ($p<0.08$), there were no significant differences in any surgical outcome measures between groups including final margin status, pancreatic fistula rate, and overall morbidity. Multivariate analysis failed to identify chronic pancreatitis as a predictive factor for any of the chosen outcome variables.

Conclusion: Despite potential for difficult dissection due to inflammatory changes in chronic pancreatitis, we found no differences in oncologic outcomes in patients undergoing pancreatectomy.

Introduction

The effects of pancreatitis on fistula formation after pancreatic resection have been presented in numerous studies [1-6]. Many of these studies have revealed a beneficial component of pancreatitis in providing a firmer parenchyma on which to sew or staple, thereby decreasing the incidence of postoperative fistula. Accordingly, the combination of a small duct and soft gland has been found to be associated with a drastically higher rate of complications relating to the pancreatic duct anastomosis in pancreaticoduodenectomy [4].

Despite the importance of avoiding pancreatic fistula, the importance of efficacy for oncologic resections is paramount to the patient's long-term outcome. Firm texture and inflammation of the pancreas in the face of chronic pancreatitis can confound accurate assessment of gross tumor margins as well as create increased friability in dissecting adjacent tissue planes [5,7]. Little data exist specifically examining the role of pancreatitis on oncologic resections.

Given these considerations, we sought to examine the impact of chronic pancreatitis on a cohort of patients undergoing resection for pancreatic malignancy.

Methods

The study was designed as a retrospective review of consecutive partial pancreatectomies performed from July 21, 2005 to July 21, 2011. Operations were performed at a university-affiliated teaching hospital by a single surgeon. Patients with benign or pre-malignant (mucinous cystadenoma, main-duct intraductal papillary mucinous neoplasm) disease were excluded.

Subjects were analyzed in groups based on the presence of chronic pancreatitis in the surgical specimen. Chronic pancreatitis was considered present if indicated on final pathology. Clinical history of pancreatitis was also elicited from the medical record. Variables collected included demographics, co-morbid conditions, surgical details, final diagnosis, need for intraoperative margin re-excision, final margin status, and 30-day postoperative morbidity and mortality. Co-morbidities were categorized by the Charlson Co-Morbidity Index (CCI) [8]. Pancreatic fistulas were graded according to the International Study Group on Pancreatic Fistula (ISGPF) classification [9]. Operatively placed drains were not routinely analyzed for amylase levels, leading to a falsely low reporting of grade A fistulas. Therefore, only grade B & C fistulas were considered. Surgical morbidities were graded by the Clavien-Dindo classification and grade III or higher were included in the analyses concerning overall morbidity [10]. Ductal size was not available for all cases and thus was not used. Small ducts, however, were managed with stents and use of ductal stent is a

generalized surrogate marker for duct size in this series. The primary outcome measures were need for margin re-excision and final margin status. Secondary outcome measures were postoperative pancreatic fistula and overall morbidity rates.

Ethics

The study received Institutional Review Board approval prior to data collection, and was performed in accordance with the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Written consent from the patients was waived by the Institutional Review Boards on the grounds of a retrospective review that did not directly benefit or harm the patient other than potential loss of confidentiality. Records were maintained in accordance with privacy standards.

Statistics

Comparisons between groups were made using chi-squared or Fisher's exact test as indicated for categorical variables and the student's *t*-test for continuous variables. A multivariate logistic regression model was used to account for age, gender, body mass index (BMI), CCI, surgical procedure, method of pancreatic transection, use of ductal stent, and final pathology. Significance was assessed for $p<0.05$.

Results

Two hundred fifty nine partial pancreatectomies were performed during the study period. One hundred five patients were excluded for benign or premalignant histology leaving 154 patients for review. The population was distributed equally by gender and had few serious co-morbidities (Table 1). The majority of patients underwent pancreaticoduodenectomy and the most common diagnosis was pancreatic adenocarcinoma.

Table I: Patient Demographics (n=154).

		N (%)
Age (mean ± SD)		65.0 ± 12.3
Gender	Female	71 (46.1%)
	Male	83 (53.9%)
BMI (mean ± SD)		27.6 ± 6.0
Charlson Co-morbidity Index	2	85 (55.2%)
	3	51 (33.1%)
	4	15 (9.7%)
	≥5	3 (1.9%)
Chronic pancreatitis	Yes	48 (31.2%)
	No	106 (68.8%)
Surgery	Pancreaticoduodenectomy	127 (82.5%)
	Distal Pancreatectomy	27 (17.5%)
Ductal stent used	Yes	41 (26.6%)
	No	113 (73.4%)
Final pathology	Pancreatic adenocarcinoma	116 (75.3%)
	Peri-ampullary adenocarcinoma	10 (6.5%)
	Cholangiocarcinoma	3 (1.9%)
	Pancreatic neuroendocrine tumor	25 (16.2%)

Forty-eight patients had evidence of chronic pancreatitis on final pathologic examination. In addition, 13 of these patients (8.4%) had a clinical history of chronic pancreatitis. Comparison between groups yielded no significant differences in presentation or treatment variables (Table 2).

Table II: Pancreatitis Groups.

	Pancreatitis*	No Pancreatitis*	p value
	(n=48)	(n=106)	
Age (mean ± SD)	66.5 ± 10.2	64.3 ± 13.2	0.32
Gender (Male)	26 (54.2%)	57 (53.8%)	0.96
BMI	27.0 ± 5.6	27.8 ± 6.2	0.45
CCI	2.7 ± 0.7	2.6 ± 0.9	0.62
Surgery (Pancreaticoduodenectomy)	41 (85.4%)	86 (81.1%)	0.52
Stent used	12 (25.0%)	29 (27.4%)	0.76
Pathology (Pancreatic adenocarcinoma)	40 (83.3%)	76 (71.7%)	0.33

Surgical outcomes are listed in Table 3. Though the percentage of patients requiring intraoperative re-excision for margins and having final positive margins was higher in the pancreatitis group, these were not statistically significant. The pancreatic fistula rate was 6.5% for the entire cohort and there were no differences between groups. Overall morbidity and mortality rates were 23.4% and 1.3%, respectively, with equal distribution amongst the two groups.

Table III: Pancreatectomy outcomes based on presence of pancreatitis; *mean ± SD; # n=37 for pancreatitis and n=79 for no pancreatitis; @ n=105 for no pancreatitis.

	Pancreatitis	No Pancreatitis	p value
OR duration*	295 ± 78	310 ± 89	0.30
Estimated blood loss*	583 ± 373	536 ± 356	0.46
Intraoperative re-excision for margins	8 (16.7%)	7 (6.6%)	0.08
Final margins positive	20 (41.7%)	32 (30.2%)	0.16
Days to tolerating diet* #	8.0 ± 3.8^	8.2 ± 4.3&	0.85
Duration of JP drainage@	7.9 ± 4.4	7.4 ± 4.5	0.50
SSI	1 (2.1%)	2 (1.9%)	>0.999
Thromboembolic event	5 (10.4%)	6 (5.7%)	0.32
Pancreatic fistula	3 (6.3%)	7 (6.6%)	>0.999
Re-exploration	1 (2.1%)	3 (2.8%)	>0.999
ICU duration*	2.1 ± 1.9	2.4 ± 3.4	0.57
ICU readmission	2 (4.2%)	4 (3.8%)	>0.999
Hospital LOS*	14.2 ± 7.9	13.7 ± 8.1	0.72
Disposition home	89 (84.0%)	34 (70.8%)	0.16
Morbidity	13 (27.1%)	23 (21.7%)	0.47
Mortality	1 (2.1%)	1 (0.9%)	0.53

Multivariate analysis revealed that the presence of chronic pancreatitis was not associated with worse outcomes for any of the chosen measures (Table 4). For intraoperative re-excision of margins, however, this was approaching statistical significance. Patients with pancreatic adenocarcinoma were far more likely to have positive final margins than those with peri-ampullary adenocarcinoma, cholangiocarcinoma, or neuroendocrine tumors (OR 6.4, 95% CI 2.1-19.7).

Table IV: Multivariate Analysis – Effect of Chronic Pancreatitis.

Outcome Variable	OR (95% CI)
Pancreatic Fistula	NS
Morbidity	NS

Intraoperative Re-excision for Margins	2.8 (0.96-8.3)
Final Margins Positive	NS

Discussion

Chronic pancreatitis has been shown to have a protective effect on the development of postoperative pancreatic fistula [4,5]. Despite this benefit, chronic inflammation may result in difficulty assessing gross margins in patients with malignant pancreatic disease and lead to a more tedious dissection [7]. In this study we analyzed 154 patients who underwent partial pancreatectomy for malignancy and though nearly one-third of patients had chronic pancreatitis, there were no differences in oncologic or standard surgical outcomes associated with this finding.

The primary goal in patients with malignant disease is to achieve an R0 resection to improve survival. This can be complicated in patients with inflammation surrounding the pancreas either from chronic pancreatitis or desmoplastic reaction. Few studies to date have specifically examined the role of chronic pancreatitis in performing oncologic resections. In our study we chose need for intraoperative re-excision of margins and positive final margins as the primary outcome measures. There were no differences in outcome measures between groups based on the presence of chronic pancreatitis, though there was a trend towards increased need for intraoperative re-excision of margins. This is likely related to difficulty in palpating or visualizing normal tissue in the face of inflammatory change and firmer pancreatic parenchyma. Despite this trend there was no difference in final margin status between groups based on the presence of pancreatitis. The only predictive factor for positive margins on final pathology was a diagnosis of pancreatic adenocarcinoma as compared to the other malignancies evaluated. Elevated R1 resection rates have been consistently reported in pancreatic adenocarcinoma and is likely indicative of early metastasis as demonstrated in animal models [11].

Reports on the rate of postoperative pancreatic fistula have varied greatly. The ISGPF has provided a concise, reproducible definition of pancreatic fistulas, allowing for standardization across studies [9]. The role of pancreatitis on fistula formation has been investigated in both pancreaticoduodenectomy and distal pancreatectomy with varying results. Risk factors for development of postoperative pancreatic fistula include obesity, increased operative blood loss, and sutured closure without main duct ligation, amongst others [6]. In studies demonstrating decreased fistula rates it has been proposed that a firmer parenchyma is protective against fistula formation. The results presented here demonstrate a low pancreatic fistula rate of 6.5%. Additionally, the study was largely comprised of patients undergoing pancreaticoduodenectomy which has been demonstrated to have a lower fistula rate than distal pancreatectomy [6]. With a low fistula rate, there were no differences in postoperative pancreatic fistula observed between patient groups based on the presence of pancreatitis in our study.

In addition to postoperative pancreatic fistula, the effect of chronic pancreatitis on other surgical morbidities is unclear. We defined postoperative morbidities in a consistent fashion using the Clavien-Dindo classification and found there was no difference in morbidity rates between groups. Additionally, mortality was equal between groups as well. Despite the operative challenges posed by increased chronic inflammation of the pancreas, it appears this has no impact on short-term surgical outcomes.

This study is limited in its analysis by the retrospective design, however, utilizing standardized definitions for postoperative morbidities allowed for reduction of observation bias. Ductal size was not specifically identified for each patient and therefore is not reported. Ductal stents were, in general, used solely in the case of small ducts and this variable serves as a surrogate marker of duct size though is not exact. Long term survival was not examined for this study, though it is unlikely that a significant impact would be seen as there were no differences in margin positivity or short-term outcomes.

Conclusions

In conclusion, 154 patients with pancreatic cancer were investigated to determine the impact of chronic pancreatitis on oncologic outcomes following partial pancreatectomy. There were no differences identified in either need for intraoperative re-excision for positive margins or final margin status. Moreover, postoperative morbidity and mortality rates were equivalent between groups. These data suggest that despite technical challenges involved in performing pancreatic surgery in patients with chronic pancreatitis, successful outcomes can be obtained without sacrificing oncologic efficacy.

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Research article Open Access

Chirurgia Cancerului Gastric–Analiza A 110 Cazuri

B Popescu[1*], **F Iordache**[1], **C Turculeț**[1], **Mihaela Vartic**[2] **and M Beuran**[1]

[1]*Departamentul X Chirurgie, Universitatea de Medicină și Farmacie "Carol Davila" București, Romania*

[2]*Departamentul de Anestezie și Terapie Intensivă, Spitalul Clinic de Urgență București, Romania*

[*]**Correspondence author:** Bogdan Aurelian Popescu MD, Str. Serg. Lăţea Gheorghe, No 5, Bl. C82, Sc. A, Ap. 27, Sector 6, Bucureşti, Romania, Tel: +40 (0) 0724 26 32 69; E-mail: drbogdanpopescu@gmail.com

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Abstract

Introduction: The current trend for the modern treatment of gastric cancer it is represented by radical surgery with extended lymphadenectomy. The lymphadenectomy, as defined by the Japanese surgeons, is an important, already proved, marker for the overall and disease free survival, but is associated with a risk of postoperative morbidity and mortality.

Aim: The aim of the study was to analyze the gastric cancer surgery evaluating the postoperative morbidity and mortality.

Material and Method: We performed an observational study, on 110 patients with gastric cancer operated in the Emergency Clinical Hospital București. We also included in our study the tumors located at the gastro-oesophageal junction (that proved by histopathology exam to be of gastric origin) and the tumors of the remnant stomach. RESULTS: The men to women ratio was 1.5 and the mean age was 65.02 ± 11.04 years old. The gastric cancer is located in the 1/3rd upper part in 20.90% cases, and on the distal 2/3rd in 68.17%. Almost half of the patients (48.18%) were admitted with complications (bleeding, stenosis and/or perforation). 25.54% from the patients had distant metastasis (liver, peritoneum, pulmonary, or/and lymphnodes). All the cases were advanced or locally advanced gastric cancer and no case of early gastric cancer has been noted. Most of our surgical interventions were standard resections: total or distal gastrectomy associated with D_1 lymphadenectomy in 64 cases and D_2 in 32 cases. The mean operative time was 182.3 ± 99 minutes. The overall mortality rate was of 4.5%. The type of lymphadenectomy wasn't a risk factor for postoperative mortality.

Conclusions: The gastric cancer is diagnosed, most commonly, in an advance stage. However, the trend is to perform radical or potentially radical gastrectomies associated with D_1 or D_2 lymphadenectomy. The type of lymphadenectomy is not a risk factor for postoperative morbidity and mortality.

Keywords: Gastric Cancer; Advanced Gastric Cancer; Gastrectomy; Lymphadenectomy

Introducere

Un studiu multicentric realizat în anul 2004 a evidențiat o prevalență a cancerului gastric (CG) în România de 2,9/100.000 de locuitori [1]. Din păcate, din lipsa unui program național de prevenție, majoritatea prezentărilor la spital a pacienților cu CG se face într-un stadiu avansat ceea ce îngreunează decizia terapeutică și intervenția chirurgicală (gastrectomie asociată cu limfadenectomie). Spitalul nostru nu face o excepție de la regulă.

Obiectivul prezentului studiu este de a evalua atitudinea chirurgilor în raport cu radicalitatea intervențiilor pentru CG.

Material Și Metodă

Au fost analizate retrospectiv protocoalele operatorii și foile de observație ale pacienților internați pentru CG în cele trei secții de chirurgie ale Spitalului Clinic de Urgență București în perioada ianuarie 2011-ianuarie 2012. S-au notat 142 de pacienți cu CG la care s-a intervenit chirurgical. Dintre aceștia, 110 au fost incluși în studiu (77,42%), restul de 32 de fiind diagnosticați histopatologic cu alte tipuri de tumori. Am inclus în studiul nostru atât localizările eso-gastrice cât și cancerul de bont gastric. Pentru înregistrarea complicațiilor postoperatorii s-a folosit clasificarea Dindo-Clavien [2].

Analiza statistică s-a realizat cu programul StatsDirect versiunea 2.7.9. S-au folosit testele chi pătrat, Fischer și testul t, cu un coeficient $\alpha<0,05$. Valorile medii au fost exprimate ca medie ± SD (standard deviation).

Rezultate

Raportul bărbați/femei a fost de 1,5 66/44, cu o vârstă medie de 65,02 ± 11,04 ani (37-86 ani) (Figure 1).

Localizările proximale (eso-gastric, cardia, fundus) au reprezentat 20,90% din cazuri (n=23) iar localizările medii și distale, 68,17% (n=75). Tumorile infiltrative (linita plastică) au fost înregistrate în două cazuri și tumorile de bont în 8 cazuri (Table 1).

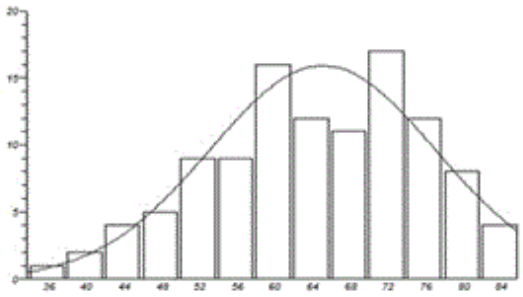

Figure 1: Distribuția pacienților pe grupe de vârstă.

Table I: Distribuția cazurilor în funcție de localizarea tumorii.

Localizare	n	%
Proximal	23	20,90
Corp gastric	36	32,72
Antru gastric	39	35,45
Linită	4	3,63
Bont gastric	8	7,27

Aproape jumătate (48,18%) din cazurile analizate (n=53) s-au prezentat cu una din complicații: hemoragie, stenoză, perforație. Hemoragiile au fost notate în 27,27% (n=30) din cazuri, stenozele, 17,27% (n=19), iar perforația într-un singur caz (0,90%). În 24,54% (n=27) din cazuri au fost constatate determinări secundare la distanță: hepatice, ganglionare, peritoneale sau/și pulmonare.

Cu o excepție (eso-gastrectomie asistată robotic), toate intervențiile chirurgicale au fost realizate prin abord clasic (laparotomie). În majoritatea cazurilor s-au realizat gastrectomii standard. Gastrectomia standard este definită ca gastrectomia totală sau distală [**3**], iar cele non-standard sunt reprezentate de: gastrectomia cu prezervare de pilor, gastrectomia polară superioară, gastrectomia segmentară, rezecțiile locale. Gastrectomia totală a fost folosită în 41,81% (n=46) de cazuri, iar cea distală în 39,09% (n=43). Printre celelalte tipuri de intervenții se numără: eso-gastrectomia totală (n=3; 3,63%), gastrectomia proximală (n=2; 1,81%), gastrectomia segmentară (n=2; 1,81%) proceduri paliative și laparotomii exploratorii (n=14; 12,72%). Într-un singur caz a fost folosit un dublu abord, abdominal și toracic (eso-gastrectomie).

Nu s-a înregistrat nici un caz de CG incipient (T_{is}, T_1 și orice N) [**4**]. Cele mai frecvente stadializări au fost: T_4 60,90% (n=67), N_2 46,36% (n=51) și respectiv M_0 75,45% (n=83) (Table 2).

Limfadenectomia D2 a fost realizată cu o frecvență mai mare în cazul gastrectomiilor totale decât în cazul gastrectomiilor distale (P=0,040). Din cazurile în care s-a realizat limfadenectomie D_2, 34,37% (n=11) au fost realizate în stadiul IIIC. Pentru toate stadiile, în afară de stadiul IB, limfadenectomia tip D_1 a fost majoritară (Table 3). Totuși stadiul tumoral nu a influențat alegerea tipului de gastrectomie sau al limfadenectomiei (P=0,688).

Limfadenectomia D_1 a fost realizată în 64 de cazuri (58,2%) iar limfadenectomia D_2 în 32 de cazuri (29,1%) și în celelalte 14 (12,72%) cazuri nu s-a realizat limfadenectomie, intervenția fiind definită ca paleativă.

Table II: Distribuția cazurilor în funcție de stadializarea TNM.

Parametru TNM	n	%
Tis/T1	0	0
T2	8	7,27
T3	35	31,81
T4	67	60,90
N0	14	12,72
N1	26	23,63
N2	51	46,36
N3	19	17,27
M0	83	75,45
M1	27	24,54
Stadiu	n	%
IB	2	1,81
IIA	10	9,09
IIB	14	12,72
IIIA	15	13,63
IIIB	11	10,00
IIIC	31	28,18
IV	27	24,54

Mortalitatea a fost de 4,5% (5 cazuri). Analizând mortalitatea în funcție de limfadenectomia efectuată am observat 3 decese în lotul celor cărora li s-a efectuat limfadenectomie tip D_1 (4,68%) și 2 decese în lotul celor cu limfadenectomie tip D_2 (6,66%) (P=0,99). În ambele decese cu limfadenectomie D_2 s-au realizat și splenectomii, dar nu și în cele cu limfadenectomie D_1.

Durata medie a operației a fost de 182,3 ± 99 min; pentru limfadenectomiile tip D_1 a fost de 204,83 ± 90 min (mediană 200 min), iar pentru gastrectomiile cu limfadenectomie tip D_2 a fost de 188,75 ± 106 min (mediană 162,5 min) (P=0,446) (Figure 2).

Complicații postoperatorii au fost înregistrate la 40 de pacienți (36,36%).

Table III: Corelație stadiu/tip de intervenție. GD gastrectomie distală; GT gastrectomie totală (au fost incluse și esogastrectomiile totale); D_1 limfadenectomie tip D_1; D_2 limfadenectomie tip D_2; * În cazul limfadenectomiilor D2 în stadiul IV s-a realizat și excizia metastazelor la distanță (metastazectomii hepatice unice); ** Au fost excluse din Table rezecțiile nonstandard, laparotomiile exploratorii, derivațiile interne.

Stadiu	GD	GT	GD	GT	Total
	+ D1		+ D2		
IB	1	0	1	0	2
IIA	4	3	0	2	9
IIB	4	4	2	4	14
IIIA	5	4	1	3	13
IIIB	5	1	0	5	11
IIIC	9	6	3	8	26
IV*	7	7	1	2	17
Total	35	25	8	24	92**

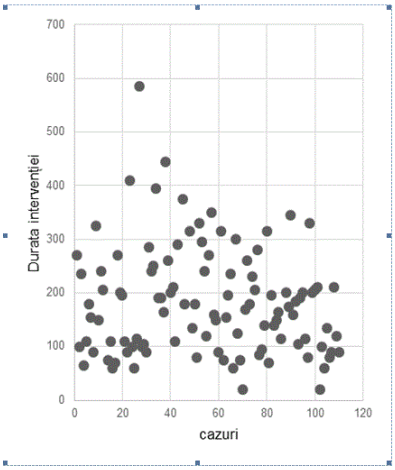

Figure 2: Durata intervenției chirurgicale (min); Se remarcă intervențiile cu durată mai mică de 30 min (laparotomii exploratorii) și respectiv gastrectomia asistată robotic cu o durată de 585 min.

Am înregistrat 10 reintervenții (Dindo-Clavien IIIb), unele dintre acestea evoluând către stadii mai mari ale clasificării Dindo-Clavien (DC).

Patru din cele 10 reintervenții au evoluat către decesul pacienților. Dintre cele 10 reintervenții (Table 4), 6 au fost pentru fistule postoperatorii (au fost notate în total 10 fistule postoperatorii). În celelalte cazuri s-a reintervenit pentru hemoragie, eviscerație, ischemie mezenterică și o gastrostomie nefuncțională (Table 4). Din cele 10 fistule postoperatorii, patru (40%) au dus la decesul pacienților. Decesele au fost notate la 2 pacienți tratatați conservator și două la cei care s-a reintervenit. Opt (80%) din cele 10 fistule au fost înregistrate după gastrectomii distale iar două, (20%) după gastrectomii totale (P=0,017). 90% dintre fistule au fost notate după limfadenectomie D1.

Table IV : Reintervențiile.

Cauza reintervenției	n	%
Fistulă anastomotică	4	3,6
Fistulă duodenală*	2	1,8
Hemoragie tardivă	1	0,9
Eviscerație	1	0,9
Ischemie mezenterică acută	1	0,9
Gastrostomă nefuncțională	1	0,9
Total	10	9,9

În funcție de tipul de gastrectomie standard folosit, au fost înregistrate 8 fistule pentru GD și 1 fistulă pentru gastrectomiile totale (P=0,017), iar în funcție de tipul tipul de limfadenectomie, 9 fistule pentru D_1 și una pentru D2 (P=0,091).

Discuții

Nu am constatat creșterea incidenței tumorilor din treimea proximală gastrică demonstrată de către unii autori [**5**]. Gastrectomia cu limfadenectomie D_2 este considerată un standard de către chirurgii asiatici (Japonia, Coreea, China), iar în ultimul deceniu tehnica tinde să fie adoptată și de chirurgii europeni și americani [**6**], deoarece îmbunătățește supraviețuirea globală și, mai ales, "disease free" [**7**,8].

Clasic se considera că limfadenectomia D_2 este asociată cu un timp operator prelungit și o morbiditate postoperatorie crescută față de limfadenectomia D_1; pe studiul prezentat nu s-a notat o diferență semnificativă statistic în acest sens, neomogenitatea lotului din punct de vedere al localizării, stadializării și tehnicii chirurgicale și posibil diferența de experiență chirurgicală între chirurgii din studiu, fiind posibile explicații [**9**]. Luna A. și colab [**10**] au demonstrat o rată acceptabilă a morbidității (47,7%) și mortalității (6,8%) în cadrul curbei de învățare a tehnicii pentru limfadenectomie D_2, condiția fiind ca tehnica să fie învățată într-un centru de excelență în chirurgia gastrică pentru cancer.

Yu X. și colab [**11**] într-un studiu din 2013, a evidențiat că limfadenectomia D_2 ar crește diseminarea tumorală peritoneală la pacienții cu CG avansat și recomandă lavajul peritoneal abundent la sfârșitul intervenției pentru a rezolva această problemă.

Pentru o stadializare corectă în timpul gastrectomiei cu limfadenectomie D_2 se recomandă o disecție chirurgicală *ex-vivo* [**12**].

În ultimii ani există tendința de a dezvolta gastrectomiile cu limfadenectomii D_2 prin abord minim invaziv, laparoscopic sau robotic, care conservă avantajele "clasice" ale limfadenectomiei dar asigură o recuperare postoperatorie mai rapidă [**8**,13]. Experiența noastră în acest sens este limitată, un singur caz beneficiind de abord minim-invaziv, robotic. Studiul lui Vasilescu C. și colab [**14**] arată că, și în România limfadenectomia D_2 tinde să devină tehnica standard pentru CG, dar recomandă ca tehnicile minim invazive să rămână apanajul centrelor supra-specializate pentru a îmbunătăți rezultatele.

Rata morbidității (46,36%) și a mortalității (4,5%) în studiul nostru a fost în limitele citate în literatură [1-10]. acceptabile.

Concluzii

Cancerul gastric este, cel mai adesea, diagnosticat în stadii avansate. Cu toate acestea, tendința actuală este de a realiza gastrectomii radicale, cu limfadenectomii D_2. Tipul de limfadenectomie (D_1 vs D_2)

nu influențează morbiditatea și mortalitatea postoperatorie dar îmbunătățește supraviețuirea.

Conflict De Interese

Autorii nu declară nici un conflict de interese.

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Cum Putem Îmbunatati Urmarirea Pacientilor Operati De Hernie Inghinala

D Moga*

Secţia Chirurgie, Spitalul Militar de Urgenţă "Dr. Alexandru Augustin" Sibiu, România

***Corresponding author:** D Moga, MD, Department of Surgery, Emergency Army Hospital, Dr. Alexandru Augustin" Sibiu, Romania, B-dul Victoriei 44-46, 550024, Sibiu, Romania, Tel: +40 (0) 269 21 12 09; E-mail: mogadoru@yahoo.com

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Abstract

Background: A long-term follow-up of inguinal hernia operated patients is mandatory in order to evaluate the efficiency of the surgical procedures. AIM: The aim of this study is to evaluate a personal follow-up procedure for the operated inguinal hernia patients.

Material and Methods: A prospective study including the patients who underwent Lichtenstein tension-free procedure was performed. A prospective follow-up to 1, 6 and 12 months using a Quality of Life (QoL) questionnaire was performed, and the results were carefully analyzed.

Results: 44 consecutive patients operated from June 2011 until May 2012 was included in the study. The median age was 60 years old and men to women ratio were 43 to 44. To 1 month postoperative check-up, 88.63% of the patients were presented and at 6 months only 31.81% from the patients were presented to the postoperative check-up, and after 12 months 58.13% of the patients answered to QoL questionnaire. In term of QoL, 76% of the patients had "excellent result" and 24% "very good result" one year after the procedure. We recorded no recurrence one year after the procedure to the patients who underwent the check-up physical exam. Even the postoperative results are outstanding, the follow-up is only satisfactory from multiple reasons, equally related to doctors, patients and medical system as well.

Conclusions: In our conditions the long term follow-up of the inguinal hernia operated patients is more likely a goal than a routine activity. Further studies and activities (e.g. a National Hernia Registry) will be necessary to improve the patients' follow-up procedure.

Keywords: Groin Hernia; Lichtenstein Procedure; Follow-Up

Introducere

Intervenţiile chirurgicale efectuate pentru diagnosticul de hernie inghinală sunt printre cele mai frecvente intervenţii practicate în serviciile de chirurgie generală. Anual pe glob sunt efectuate aproximativ 20 de milioane de astfel de operaţii [1]. Numărul lor foarte mare este explicat prin riscul de a face o hernie inghinală de-a lungul vieţii, care este de 27% în cazul bărbaţilor şi de 3% în cazul femeilor [2]. Au fost descrise peste 70 de tehnici de cură herniară [3]. Dintre acestea însă, sunt validate în prezent un număr restrâns de intervenţii care şi-au demonstrat eficienţa: tehnica Lichtenstein, Shouldice, tehnicile laparoscopice.

Eficienţa unui procedeu chirurgical este dată de rata complicaţiilor postoperatorii (mai ales incidenţa durerii cronice) şi rata recidivei [4,5]. În acest scop urmărirea postoperatorie a pacienţilor este obligatorie.

Scopul studiului de faţă este de a evalua dacă maniera în care se efectuează urmărirea pacienţilor în serviciul nostru este corectă şi suficientă.

Material şi Metodă

În Secţia Chirurgie a Spitalului Militar de Urgenţă Sibiu, în intervalul iunie 2011 – mai 2012, au fost incluşi în studiu toţi pacienţii internaţi cu diagnosticul de hernie inghinală, operaţi de către autorul articolului. În perioada mai sus menţionată, au fost practicate 44 de operaţii protetice, prin abord anterior, după tehnica Lichtenstein.

Înainte de operaţie, cu ocazia anamnezei şi a semnării consimţământului informat, am încercat să explicăm pe înţelesul pacienţilor ce înseamnă hernia inghinală şi în ce constă intervenţia chirurgicală, cu riscurile şi complicaţiile acesteia. În scopul unei cât mai bune informări a pacienţilor, am elaborat un ghid al pacientului (*Ghidul pacientului – Ce este hernia inghinală?*), care a fost pus la dispoziţia tuturor pacienţilor care şi-au exprimat disponibilitatea de a-l parcurge.

Pacienţii operaţi, înainte de externare au fost informaţi cu privire la necesitatea controalelor postoperatorii (la 1 lună, la 6 luni şi la 12 luni postoperator), aceste informaţii fiind trecute şi în biletul de ieşire din spital/scrisoarea medicală.

Pentru evaluarea rezultatelor, chestionarele au fost interpretate utilizând următoarea scală: 9-10 puncte (*rezultat excelent*), 6-8 puncte (*rezultat foarte bun*), 5-6 puncte (*bun*), 3-4 puncte (*slab*), < 3 puncte (*foarte slab*) [6].

La controlul de 1 an, pe lângă consult pacienţii au fost rugaţi să completeze şi un chestionar (Tabelul 1). Chestionarul a fost trimis prin poştă după 1 an de la operaţie pacienţilor care nu s-au prezentat la control.

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Tabel I: Chestionar de evaluare calitativă şi cantitativă a calităţii vieţii la 1 an după cura herniei inghinale.

1) Cum vă simţiţi după cura herniei ?	
Mai rău ca înainte	**- 1**
Rău	**0**
La fel	**1**
Bine	**2**
Foarte bine	**3**
Excelent	**4**
2) Aveţi vreuna din suferinţele pe care le-aţi avut înainte de operaţie?	
Da	**0**
Nu	**1**
Dacă *Da* care ? ……..	
3) Aţi dezvoltat vreun simptom sau vreo complicaţie pe care nu aţi avut-o înainte de operaţie?	
Da	**0**
Nu	**1**
Dacă *Da*, care dintre ele:	
- atrofie testiculară (micşorarea testicolului de partea operată)	
- durere cronică	
- migrarea plasei	
- fistulă cutanată (infecţie cronică)	
Când a apărut ? specificaţi intervalul de timp scurs de la operaţie în luni: …….....	
4) S-a îmbunătăţit activitatea fizică după operaţie?	
Da	**1**
Nu	**0**
5) Sunteţi satisfăcut de operaţie ?	
Da	**1**
Nu	**0**
Dacă *Nu*, specificați de ce: ……..	
6) Aţi recomanda operaţia unui cunoscut ?	
Da	**1**
Nu	**0**
Dacă *Nu*, specificați de ce: ……..	
7) Hernia inghinală a recidivat?	
Da	**1**
Nu	**0**
Dacă *Da*, la ce interval de timp de la operație? …….....	

Rezultate

Au predominat pacienţii de sex masculin (43 din cei 44 de pacienţi). Vârsta pacienţilor a fost între 19 şi 90 de ani, 33 dintre aceştia (75%) având peste 50 de ani. Vârsta mediană a pacienţilor a fost de 60 de ani. Pacienţii au provenit din judeţul Sibiu (36 de pacienţi – 81,81%) şi judeţele limitrofe: Vâlcea (4 pacienţi – 9,09%), Alba (3 pacienţi – 6,81%), Mureş (1 pacient – 2,27%). Ca şi mediu de proveniență 27 dintre pacienţi au fost din mediul urban (61,36%) şi 17 din mediul rural (38,63%).

Au fost 38 de cazuri de hernie primară unilaterală, 2 cazuri de hernie primară bilaterală (operate în acelaşi timp operator) şi 4 cazuri de hernie recidivată unilaterală (după procedee tisulare, retrofuniculare).

Pe perioada urmăririi postoperatorii, cu ocazia controalelor am diagnosticat un hidrocel şi 2 hernii inghinale primare, pe partea controlaterală. Nu a fost diagnosticată nici o recidivă herniară. Unul dintre pacienţi a decedat la 10 luni de la operaţie, fără legătură cu intervenţia chirurgicală.

Prezenţa pacienţilor la controale a fost următoarea: la 1 lună 39 de pacienţi din 44 (88,63%), la 6 luni 14 pacienţi din 44 (31,81%), iar la 1 an doar 9 pacienţi din 43 (20,93%). Adăugând la controlul de 1 an şi pacienţii care au răspuns la chestionarul expediat prin poştă (16 chestionare primite), am considerat că am reuşit să urmărim la 1 an 25 dintre pacienţii lotului nostru (58,13%) (Figure 1).

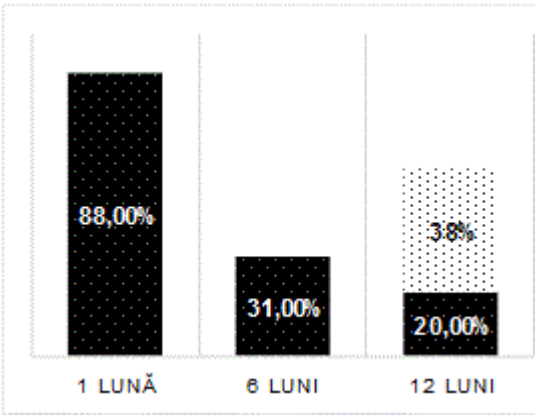

Figure 1: Distribuția pacienților în funcție de prezentarea la control. De notat procentul de 38% de pacienți care au trimis chestionarele prin poștă.

În urma interpretării chestionarelor, 19 pacienți (76%) s-au încadrat în categoria *rezultat excelent* (9-10 puncte) iar restul de 6 (24%) în categoria *rezultat foarte bun* (6-8 puncte).

Întrucât numărul de pacienţi prezentaţi la controlul de la 12 luni a fost redus, am analizat la acest interval şi pacienţii care au răspuns prin poştă la chestionar. Complianţa la follow-up din lotul total de pacienţi a crescut odată cu vârsta: < 40 de ani 2 pacienţi din 9 (22,22%),

categoria 40-60 ani 5 pacienţi din 11 (45,45%), > 60 de ani 18 pacienţi din 25 (72%).

Ca mediu de proveniență, au răspuns la controlul de 1 an 61,53% dintre pacienţii din mediu urban (16 pacienţi din 26) şi 52,94% dintre pacienţii din mediu rural (9 pacienţi din 17). 63,15% dintre pacienţii având domiciliul în municipiul Sibiu se regăsesc printre pacienţii controlaţi la 1 an.

Discuţii

Din multitudinea de tehnici chirurgicale descrise de cură herniară, în prezent s-au selectat un număr redus de procedee ale căror rezultate justifică folosirea lor [2]. Simplificând şi sintetizând şi mai mult lucrurile putem afirma că în prezent, ştiinţific validate şi recomandate pentru aplicare clinică nu au mai rămas decât 3 tehnici: tehnica tisulară Shouldice, tehnica protetică prin abord anterior Lichtenstein şi tehnicile protetice prin abord endoscopic/ laparoscopic (TEP/TAPP) [1].

Pentru a putea vorbi de rezultate competitive în ceea ce priveşte patologia herniară este necesar un lot mare de pacienţi, cu un procent înalt de pacienţi urmăriţi (85-90%), pe o perioadă lungă de timp (de preferat 5-10 ani) [7,8].

În România, se pune prea puţin accent pe importanţa urmăririi post-operatorii. În aceste condiţii, eforturile individuale de urmărire a loturilor de pacienţi, au şanse mici de reuşită, în condiţiile în care pacientul şi anturajul acestuia nu sunt familiarizaţi cu importanţa controalelor periodice. Acest fapt explică subdiagnosticarea sindromului de durere cronică postherniorafie şi că nu se poate stabili procentul real de recidivă herniară. Deşi sună mai degrabă anecdotic, unii dintre chirurgi cred că, dacă pacientul nu se prezintă la control, înseamnă că e bine".

Nu există procedeu chirurgical herniar infailibil, care să nu aibă recidive. Este însă necesar să practicăm un procedeu, care să aibă un risc cât mai mic de recidivă. Procentul de recidivă este influenţat de tehnica folosită, de experienţa operatorului, metoda şi de durata de timp pe care se face urmărirea [9]. Dacă pentru procedeele consacrate, defectele de tehnică chirurgicală sunt principala cauză de recidivă, folosirea procedeelor istorice reprezintă în sine cauză de recidivă [10].

În lipsa unei urmăriri corecte, cădem cu uşurinţă pradă unor speculaţii prin care credem că şi pacienţii noştri vor avea un risc de recidivă "ideal" (recurenţa herniară este de <1% în clinicile specializate în chirurgia parietală) sau eventual putem să credem că nu avem recidive. Aceasta în condiţiile în care se estimează că recidiva după procedeele tisulare istorice atinge 35% [3].

Cea mai fidelă metodă de urmărire postoperatorie a pacienţilor este prin examinare directă, de către chirurg. Urmărirea trebuie să fie făcută pe termen lung, acest lucru fiind îngreunat de faptul că complianţa pacienţilor scade cu timpul. Dacă pacientul nu se prezintă din proprie iniţiativă la control, care sunt soluţiile? Efectuarea de vizite periodice la domiciliu, metodă folosită de către unele servicii de chirurgie herniară, în condiţiile noastre o considerăm utopică. Alte opţiuni sunt cele legate de expedierea unui chestionar prin poştă (inclusiv poşta electronică) şi respectiv apelul telefonic (răspunderea la întrebările unui chestionar) [11]. Aceste metode sunt utile, dar cu un grad înalt de subiectivitate, putând duce la rezultate incomplete, uneori incorecte, legate de modul în care sunt redactate întrebările şi de nivelul cunoştinţelor medicale al pacienţilor. Comparând cele 2 metode indirecte de follow-up se consideră că prin apel telefonic procentul de pacienţi urmăriţi este superior celui prin chestionar, întrucât o scrisoare este mai uşor ignorată [12]. Dacă pacientul este contactat telefonic în locul chestionarului este de preferat programarea unei consultaţii. În situaţia pacientului care nu mai locuieşte la adresa cunoscută şi nu poate fi contactat telefonic, s-ar putea încerca obţinerea datelor de contact şi informaţii despre pacient de la medicul de familie [9].

Dificultăţile în urmărirea pacienţilor operaţi pentru hernie inghinală sunt multifactoriale, fiind legate de chirurg, de pacient, de sistemul medical:

Cauze legate de chirurg

- nu cheamă pacientul la control sau recomandă doar controlul la nevoie;
- nu explică pacientului importanţa controalelor;
- nu acordă timp şi atenţie suficientă pacientului prezentat la control, astfel încât pacientul nu mai revine la controalele ulterioare;
- nu ţine evidenţa controalelor;
- operaţia de hernie, cunoscută ca operaţia "rezidentului", frecvent nu este privită cu seriozitatea necesară, astfel încât nici urmărirea nu poate fi privită altfel;
- schimbarea locul de muncă (serviciul chirurgical, oraşul, ţara);
- nu ne informăm colegii că le-am operat recidivele.

Cauze legate de pacient

- nu a venit la consultaţia e control programată;
- se simte bine şi nu înţelege utilitatea controlului;
- nu se simte bine şi decide să se adreseze altui chirurg;
- nu se simte bine şi refuză ajutorul medical;
- locuieşte la distanţă de locul în care a fost operat;
- schimbarea localităţii de domiciliu;
- suferă de alte afecţiuni care îl împiedică să respecte programul controalelor;
- decedează.

Legate de system

- rata recidivelor, procentul de pacienţi urmăriţi nu reprezintă un criteriu de evaluare a calităţii serviciilor medicale;
- pacientul nu este obligat de casa de asigurări să se prezinte la controalele recomandate de către medicul specialist;
- lipsa unui sistem de secretariat pentru efectuarea apelurilor telefonice, expedierea corespondenţei;
- medicul de familie, care cunoaşte din scrisoarea medicală calendarul vizitelor, nu trimite pacientul la control;
- lipsa unui registru naţional de hernii.

În condiţiile în care folosim un procedeu actual pentru patologia herniară şi îl executăm corect, identificarea şi asumarea propriilor recurenţe herniare (într-un procent de < 5%) nu denotă lipsa de experienţă, fiind mai degrabă o dovadă de maturitate. Este necesar să ne aliniem recomandărilor ghidului european, pentru a putea oferi pacienţilor noştri servicii medicale de calitate.

Încercând să facem un profil al pacientului pe care ne aşteptăm să putem să-l urmărim postoperator, pe termen mediu şi lung, afirmăm

că este un pacient de sex masculin, de peste 60 de ani, care locuieşte la oraş (în Sibiu sau în oraşele apropiate).

Privitor la ghidul pacientului, pe un alt lot de 100 de pacienţi, 37 dintre aceştia nu au dorit să-l citească. Explicaţiile au fost multiple, dintre care menţionez "teama de a nu afla prea multe informaţii" sau dimpotrivă, că cunosc în detaliu afecţiunea de care suferă". Procentul de peste o treime dintre pacienţii care nu-şi doresc să parcurgă materialul de informare al secţiei spune multe despre nevoia concetăţenilor noştri de a fi informaţi, de a dori să înţeleagă afecţiunea de care suferă, de a avea aşteptări corecte înaintea operaţiei.

Rezultatele obţinute de către noi în prezentul studiu sunt modeste în privinţa procentului de pacienţi urmăriţi la 1 an, astfel încât nu suntem îndreptăţiţi să susţinem că nu avem recidive herniare.

Concluzii

În condiţiile actuale, urmărirea riguroasă pe termen lung a pacienţilor operaţi de hernie inghinală este o obligativitate, dar rămâne mai degrabă un deziderat decât o activitate de rutină şi un standard în serviciile chirurgicale din România.

- Soluţii pentru îmbunătăţirea rezultatelor şi a urmăririi pacienţilor ar fi:
- informarea mai detaliată a pacienţilor în privinţa afecţiunii, variantelor tehnice de rezolvare chirurgicală, a importanţei urmăririi postoperatorii;
- introducerea în contractul asigurărilor de sănătate a obligativităţii prezentării pacientului la controalele postoperatorii recomandate;
- creşterea disponibilităţii chirurgilor faţă de controalele postoperatorii;
- abandonarea procedeelor istorice neperformante;
- respectarea în detaliu a principiilor tehnicii chirurgicale folosite;
- creşterea procentului de intervenţii protetice;
- promovarea chirurgiei laparoscopice herniare;
- adoptarea *Ghidului de tratament al herniei inghinale* elaborat de Societatea Europeană de Hernie;
- crearea Registrului Naţional de Hernii.

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Conflict de Interese

Autorul nu declară nici un conflict de interese.

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Journal of Surgery
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Research Article Open Access

Hemoglobin Trend in Critically Ill Patients with Long ICU Stay

Ioana Grigoras[1,2*], **Oana C Chelarescu**[3], **Daniel M Rusu**[2] **and Irina Ristescu**[1]

[1]*University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Romania*

[2]*Anesthesia and Intensive Care Department, Regional Institute of Oncology, Iasi, Romania*

[3]*Anesthesia and Intensive Care Department, Centre Hospitalier Universitaire Caen , France*

[*]**Correspondence author:** Ioana Griogras, MD, PhD, Associate Professor of Anesthesia and Intesnsive Care, Anesthesia and Intensive Care Department, Regional Institute of Oncology, Iasi, Romania, General Henri Mathias Berthelot Street, No 2-4, 700483, Iasi, Romania, Tel: +40 (0) 374 27 88 10 ; E-mail: ioana.grigoras.ro@gmail.com

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Abstract

Introduction: Critically ill patients develop anemia due to several reasons: bleeding prior or during intensive care unit (ICU) stay, frequent flebotomies, hemodilution and inflammatory status with altered erythropoiesis. The aim of this study was to assess the trend of hemoglobin (Hb) level during long ICU stay (more than 7 days) in transfused and nontransfused patients.

Materials and Methods: We conducted a prospective observational study that included all patients with long ICU length of stay (LOS) admitted during 1 year in a 19-beds mixed ICU of a tertiary care university hospital. Patients were divided into two groups: never transfused (NT) and ever transfused (ET) according to their transfusional status during ICU stay. Collected data: demographic data, severity scores, Hb values during ICU stay transfusion status and outcome. Statistical analysis was conducted with SPSS 15.0.

Results: 132 patients (54 NT, 78 ET) were enrolled in the study. On ICU admission, overall mean Hb level was 9.2 g% (95%CI 8.72-9.72) with a significant difference between NT and ET group (10.1 g% versus 8.5 g%; p<0.01). By the day 7 there was little change in overall mean Hb value (9.1 g%; 95%CI 8.85-9.43) as in NT group the Hb values continued to drop while in ET group raised as a result of transfusions. However, at two weeks after ICU admission there was a significant decrease in mean Hb value, from 9.2 g% in day 1 to 8.1 g% (95%CI 7.71-8.49) in day 14. The variance also had a significant decrease over time (8.94 in day 1; 1.58 in day 14) indicating a convergence of Hb values in studied patients, regardless of their transfusion status.

Conclusions: Despite the fact that Hb values on ICU admission may vary widely, after 14 days of ICU stay the Hb values tend to converge. The Hb level in critically ill patients with long ICU stays decreases stadly over time no matter the transfused or non-transfused status.

Keywords: Critical Ill Patients; Anemia; Transfusion; Hemoglobin; Intensive Care

Introduction

Anemia, highly prevalent (75-98%) in critically ill patients, is associated with increased health care resource use and may be associated with poor patient outcomes [1]. Hemoglobin levels continue to drop during ICU stay [2].

Critically ill patients develop anemia due to several reasons: bleeding prior or during Intensive Care Unit (ICU) stay, frequent phlebotomies, inflammatory status with altered erythropoiesis, hemodilution [3-7]. The most common treatment of anemia in critically ill patients is blood transfusions. Taking into account the benefits and risks of transfusion, the decision to transfuse or not is a matter of continuous debate [3,4,7-9]. Despite the fact that hemoglobin (Hb) levels and transfusion practices have been the aim of many studies, most of them characterize the ICU patients with short-to-moderate Length of Stay (LOS) or particular groups of ICU patients [4,7,9,10]. For critically ill patients with prolonged ICU stay such data are still needed. Moreover, evidences suggest that a greater Hb variability overtime is independently associated with a higher mortality rate in end stage renal disease patients [11]. The aim of our study was to assess the trend of hemoglobin value in critically ill patients with long ICU LOS (more than 7 days) with respect to transfusion status.

Material and Methods

We conducted a prospective, single center observational study in a 19-beds mixed ICU of an adult tertiary care hospital, over one year. Patients admitted to ICU were critically ill, surgical, medical or trauma patients. All patients admitted to ICU during a 12 months period, with a continuous length-of-stay (LOS) of more than 7 days were enrolled in the study (132 patients). For each patient demographic data (age, gender, admission type), Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Sequential Organ Failure Assessment (SOFA) scores, daily hemoglobin values and transfusion status were recorded. For all transfused patients, further information regarding transfusion trigger, number of red blood cells (RBC) units during each transfusion event and ICU LOS before first transfusion were collected. Outcome variables including ICU LOS and mortality were recorded.

Patients were divided into two groups: never transfused (NT - 54 patients; 40.9%) and ever transfused (ET-78 patients, 59.1%).

Statistical analysis was conducted using SPSS version 15.0 for Windows and Microsoft Office Excel. Continuous variables were summarized as mean ± Standard Deviation (SD) for normally and non-normally distributed variables. Comparisons between ET and NT patients were conducted using Student's *t*-test or Wilcoxon's test for normally and non-normally distributed continuous variables, respectively. $\chi 2$ or Fisher's exact test were used to compare categorical variables. 95% reference range (95% RR) and 95% confidence interval (95% CI) were calculated for the mean hemoglobin values on admission and sequentially after (day 7, 14 and 21). Kernel curves for the hemoglobin values on admission and day 14 were drawn and variance was calculated.

Results

During 12 months study period 132 patients with more than 7 days ICU LOS were enrolled. The average age in the study group was 62.8 ± 16.5 years old. The majority of patients were men (59.1%) admitted to the ICU for surgical reasons (82.6%). Mean APACHE II and SOFA scores on admission were 17.2 ± 8.2 and 5.8 ± 2.9 respectively. Overall, mean ICU LOS was 12.9 ± 5.5 days and mortality rate reached 47%. More than half of the critically ill patients with long ICU LOS (78 patients, 59.1%) received one or more red blood cells (RBC) units during their ICU stay.

No statistical differences regarding age, admission type and severity scores on admission were found between the NT and ET groups. However, patients receiving transfusions had higher SOFA scores later on during ICU LOS. Mean "worst" SOFA score was 9.8 ± 4.5 in ET group versus 8.9 ± 3.6 in NT group (P=0.04). Mortality rate was also found to be higher in patients receiving transfusions when compared to non-transfused patients (65.4% versus 20.4%; P=0.04). Baseline information regarding demographics data and outcome variables of patients enrolled in the study are summarized in Table 1.

Table I: Patient's data.

	All Patients	Never Transfused	Ever Transfused	P Value
	132 (100%)	54 (40.9%)	78 (59.1%)	
Age (years) – mean ± SD	62.8 ± 16.5	65.7 ± 14	60.4 ± 17.6	0.07
Gender male - no.(%)	78 (59.1%)	30 (55.6%)	48 (61.5%)	0.48
Admission type - no.(%)				
surgery	109 (82.6%)	49 (90.7%)	60 (76.9)	0.56
emergency	73 (55.3%)	33 (61.1%)	40 (51.3%)	0.88
elective	36 (27.3%)	16 (29.6%)	20 (25.6%)	0.45
medical	18 (13.6%)	5 (9.3%)	13 (16.7%)	-
trauma	5 (3.8%)	0 (0%)	5 (6.4%)	-
Severity of the disease				
APACHE II on admission -mean ± SD	17.2 ± 8.2	16.9 ± 8.3	17.4 ± 8.1	0.36
APACHE II worst - mean ± SD	22.7 ± 9.7	23.3 ± 9.5	22.2 ± 9.8	0.58
SOFA on admission - mean ± SD	5.8 ± 2.9	5.5 ± 3	6.2 ± 2.8	0.83
SOFA worst - mean ± SD	9.4 ± 4.1	8.9 ± 3.6	9.8 ± 4.5	0.04
Outcome				
ICU LOS (days) - mean ± SD	12.9 ± 5.5	12.8 ± 4.6	13 ± 6.1	0.88
ICU mortality - no. (%)	62 (47%)	11 (20.4%)	51 (65.4%)	0.04

The 78 patients of ET group were transfused in 154 different occasions with one or more RBC units. Half of them (51.3%) were transfused in the first 24 hours after ICU admission, and only 6.4% had their first transfusion after one week of ICU stay. Mean transfusion trigger Hb was 7.8 ± 2.3 g%. Most of the patients received 3 units of RBC in 2 different occasions and had a mean Hb increase of 0.9 g% after each transfusion event. Transfusion requirements during ICU LOS were higher in the first 2 days following admission and decreased after this period. The total number of RBC units used during the 12 months study period for critically ill patients with long ICU stay was 228. The informations regarding transfusion policy are summarized in Table 2.

Table II: Transfusion policy.

ICU LOS before first transfusion - no. of pts (%)	
<1 day	40 (51.3%)

1-7 days	33 (42.3%)
> 7 days	5 (6.4%)
Transfusion trigger Hb (g%) - mean ± SD	7.8 ± 2.3
Transfusion events/pacient - mean ± SD	2 ± 1.2
RBC units transfused/patient - mean ± SD	2.9 ± 2.4
Post transfusion Hb (g%) - mean ± SD	8.3 ± 1.9
Mean Hb increase/transfusion event - g%	0.9
78 ever transfused patients;154 transfusion events – 228 RBC units	

Overall, mean Hb value on admission was 9.2 ± 3 g%. There was a statistically significant difference in mean Hb on admission in NT patients versus ET patients (10.1 g% versus 8.5 g%; P<0.01). However the prevalence of anemia (Hb<12 g%) on ICU admission was high in both groups (74.1% in NT patients, 89.7% in ET patients). Moderate and severe anemia on admission had higher prevalence rates in transfused than in non-transfused patients (moderate anemia 21.8% versus 13%; severe anemia 20.5% versus 7.4%, respectively) without reaching statistical significance (P=0.84 and P=0.93 respectively). Prevalence of anemia on ICU discharge was even higher than on admission (95.4% compared to 83.3%, P<0.01) both in the NT (94.4% versus 74.1%, P<0.01) and ET patients (96.1% versus 89.7, P=0.2). Table III summarizes these data.

Table III: Prevalence of anemia.

	All Patients	Never Transfused	Ever Transfused	P Value
	132 (100%)	54 (40.9%)	78 (59.1%)	
Hb (g%) on ICU admission - mean ± SD	9.2 ± 3	10.1 ± 3.3	8.5 ± 2.8	<0.01
Anemia – on ICU admission - no.(%)	110 (83.3%)	40 (74.1%)	70 (89.7%)	0.11
Hb=12 - 8 g%	66 (50%)	29 (53.7%)	37 (47.4%)	0.14
Hb=7,9 - 6 g%	24 (18.2%)	7 (13%)	17 (21.8%)	0.84
Hb<6 g%	20 (15.1%)	4 (7.4%)	16 (20.5%)	0.93
Hb (g%) on ICU discharge - mean ± SD	8.5 ± 1.9	8.6 ± 1.9	8.4 ± 1.9	0.47
Anemia - at ICU discharge - no.(%)	126 (95.4%)	51 (94.4%)	75 (96.1%)	0.64
Hb=12 - 8 g%	74 (56.1%)	32 (59.2%)	42 (53.8%)	0.82
Hb=7,9 - 6 g%	43 (32.6%)	15 (27.8%)	28 (35.9%)	0.13
Hb<6 g%	9 (6.8%)	4 (7.4%)	5 (6.4%)	0.18

ICU course of Hb levels, according to admission Hb range, as well as the trend of mean Hb value in transfused and non-transfused patients, reveals the tendency of convergence toward a value a little higher than the transfusion trigger (Figures 1 and 2).

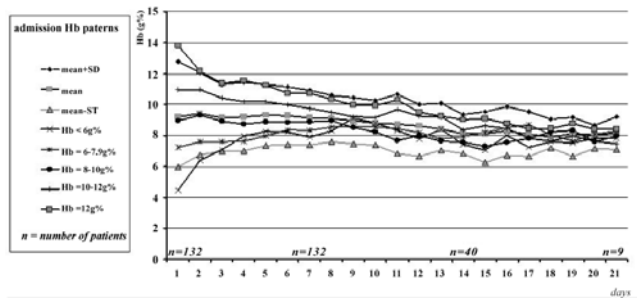

Figure 1: ICU course of Hb levels according to admission Hb range.

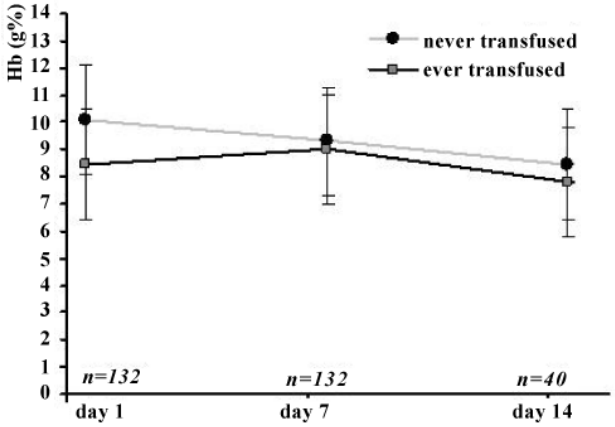

Figure 2: ICU course of mean Hb level in NT and ET groups.

On admission mean Hb level was 9.2 g% (95% CI 8.72-9.72) with a significant difference between NT and ET group (10.1 g% versus 8.5 g

%; P<0.01). By the day 7 there was little change in mean Hb value (9.1 g%; 95%CI 8.85-9.43) as in NT group the Hb values continued to drop while in ET group raised as a result of transfusions. However, at two weeks after ICU admission there was a significant decrease in mean Hb value, from 9.2 g% in day 1 to 8.1 g% (95%CI 7.71-8.49) in day 14. The variance also had a significant decrease over time (8.94 in day 1; 1.58 in day 14) indicating a convergence of Hb values in studied patients, regardless of their transfusion status. The convergence of Hb levels over time, no matter the transfusion status or admission Hb level is shown by the Kernel curves of distribution of Hb values in 1st day and 14th day of ICU LOS (Figure 3).

Discussion

Our study evaluated the time course of Hb values in critically ill patients with long ICU LOS. All patients with more than one week of ICU LOS were followed up, no matter the transfusion status. Other studies had already revealed that Hb concentration decreases over time during ICU stay [3,4,7,12]. Most of them concern all ICU patients no matter the duration of ICU LOS.

As other authors, we found a high prevalence of anemia on ICU admission that persisted during ICU LOS [3,7,12-14]. This could be partially explained by the restrictive blood transfusion policy applied in our ICU, mean ± SD transfusion trigger Hb being 7.8 ± 2.3 g%.

Transfusion requirements during ICU LOS were higher in the first 2 days following admission. One reason might be the high proportion of surgical patients included in our study. Another explanation is the necessity of a complete evaluation of a patient on ICU admission which involve placement of invasive devices and frequent phlebotomies.

Time course of Hb levels revealed a tendency of convergence to a value a little higher than the transfusion trigger. This seems to be explainable as the drop in the Hb concentration over time in NT patients was never compensated as they didn't reach the transfusion trigger Hb, while in the ET patients; transfusions were used only when the risk of decreased oxygen carrying capacity was considered to exceed the risk of transfusion. However, this is not the only possible explanation as there was a significant drop in transfusion requirements in the first week of ICU stay. Persisting inflammation in critically ill patients with long ICU LOS might be another cause for sustained anemia [1,15,16]. As the outliers may have a significant influence on the results when analyzing the trend of mean Hb value over time in a group drawn from a population, we tried to overcome this problem by analyzing the variance and the Kernel curves of distribution of Hb concentrations in patients enrolled in the study. Another factor that might influence the data, the unavoidable fall in the number of patients over time, was minimized by choosing the day 14 as a comparing point for the admission Hb variance in studied patients, as after this day there was an unacceptable low number of patients for comparison. The fact that the variance also had a significant decrease over time (8.94 in day 1; 1.58 in day 14) clearly reflects that in critically ill patients with long ICU stay there is a tendency of convergence of Hb levels to a value a little higher than the transfusion trigger Hb no matter the transfusion status.

Recent observational studies do show an important adverse effect of RBC transfusion on mortality, but even the best conducted adjustments for confounding cannot completely eliminate its impact [10,17]. In our study we found no difference on the severity of the disease on admission between groups, as reflected by APACHE II and SOFA scores. However transfused patients had higher SOFA scores during their ICU LOS and a higher mortality rate.

Conclusions

Based on our results, we conclude that despite the fact that Hb values of critically ill patients may vary widely at ICU admission, after 14 days of ICU stay the Hb values tend to converge to a level closed to the transfusion trigger Hb, no matter the transfusion status. The ICU LOS and transfusion policy influence the Hb level of patients at ICU discharge.

Conflict of Interests

Authors have no conflict of interests to disclose.

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Case Report Open Access

A Rare Cause of Intestinal Perforation in a Patient on Continuous Ambulatory Peritoneal Dialysis Therapy: Abdominal Cocoon Syndrome

Berhan Genç[1*], Seyhan Yalaz[2], Atilla Çökmez[2], Aynur Solak[1] and Erkan Yılmaz[1]

[1]*Şifa University School of Medicine, Department of Radiology, İzmir, Turkey*

[2]*Şifa University School of Medicine, Department of General Surgery, İzmir, Turkey*

[*]**Corresponding author**: Dr. Berhan Genç, Department of Radiology, Şifa University, İzmir,Turkey Fevzipaşa Boulevard, No: 172/2 Basmane 35240, İzmir/Türkiye, Tel: +90- 232- 4460880/+90-533-5441328; Fax: +902324460770; E-mail: berhangenc@gmail.com

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Abstract

Abdominal Cocoon Syndrome (ACS) or sclerosing encapsulating peritonitis is characterized by intestinal obstruction and ileus as a result of encasement of small intestines totally or partially by a thick fibrous sac. We herein present a patient undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD) therapy for chronic renal failure for 3 years who developed intestinal obstruction and perforation and was subsequently diagnosed with abdominal cocoon syndrome. Abdominal cocoon should be remembered in patients on CAPD therapy. One should also be aware that clinical signs of peritonitis may not become evident in the case of intestinal perforation in patients with ACS. In such cases, computed tomography has an important role in making the diagnosis.

Keywords: Abdominal cocoon syndrome; Computed Tomography; Continuous ambulatory peritoneal dialysis

Introduction

Abdominal cocoon or sclerosing encapsulating peritonitis is a rare cause of small intestinal obstruction caused by encasement of small intestines by a thick fibrotic capsule at varying lengths [1-3]. Its exact cause is not known. It has two types as primary and secondary. The primary form is seen in pubertal girls in tropical or subtropical countries. The secondary form is more common than the primary from. Although many factors are held responsible from the secondary form, it is most commonly seen in patients with chronic renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD) treatment [1]. Cessation of CAPD by diagnosing ACS early will prevent further complications associated with this syndrome. An early diagnosis coupled with adequate treatment avoids the need of future surgical therapies including intestinal resection [4,5]. However, the diagnosis of the ACS is challenging owing to its nonspecific symptoms. Computed tomography is beneficial for diagnosis. We herein present a patient undergoing CAPD therapy for chronic renal failure for 3 years who developed intestinal obstruction and perforation and was subsequently diagnosed with ACS.

Case Report

A 52-year-old male patient presented with colic abdominal pain, nausea and vomiting for 1 week. He told that he had similar episodes in the preceding months. He, however, did not receive a specific therapy since his symptoms abated spontaneously. His past history was remarkable for CAPD therapy for chronic renal failure for the last 3 years. However, he began to undergo hemodialysis treatment owing to ineffective CAPD sessions for the past 2 months due to recurrent attacks of peritonitis. He had no history of a previous abdominal surgery. Abdominal examination was notable for upper quadrant pain. His laboratory tests revealed normal electrolytes, a mild anemia, hypoalbuminemia, and mildly increased C-reactive protein level. BUN and creatinine levels were high, consistent with end-stage renal failure. Abdominal ultrasonography demonstrated cholelithiasis and thickening of the gallbladder wall. Considering the recurrent peritonitis attacks, cholecystectomy was performed from a mini subcostal incision. Gallbladder was severely edematous. Due to diffuse and severe adhesions, abdominal cavity could not be explored. The patient was discharged with full recovery 2 days later. However, he admitted to the hospital 2 days after discharge with abdominal pain, nausea, and vomiting. On physical examination a mild abdominal distention and increased bowel sounds were noted. An abdominal Computed Tomography (CT) with contrast revealed mildly dilated, conglomerated small intestinal loops encased by a membrane as well as moderate amount of ascites surrounding the intestinal loops (Figures 1a and b). Under the light of these findings a provisional diagnosis of abdominal cocoon was made. The patient began to be monitored with the diagnosis of sub-ileus and oral feeding was stopped. At the second hospital day he developed respiratory distress and thoracic and abdominal CTs were obtained, which showed signs of intestinal perforation. An emergency laparotomy was performed. During the operation it was noted that all intestinal segments were encased by a hard fibrous sac. That fibrous structure encased the entire abdominal cavity that contained about five liters intestinal contents and gas (Figures 2a and b). Intestinal contents oozed through a point on the fibrous sac. The sac was opened and all intestinal loops were exposed by resecting some loops. A perforation was noted 15 cm proximal to the ileocecal valve. The ileum was resected for approximately 1 meter and an end ileotomy was performed. The patient developed postoperative sepsis and died 12 days later from multi-organ failure.

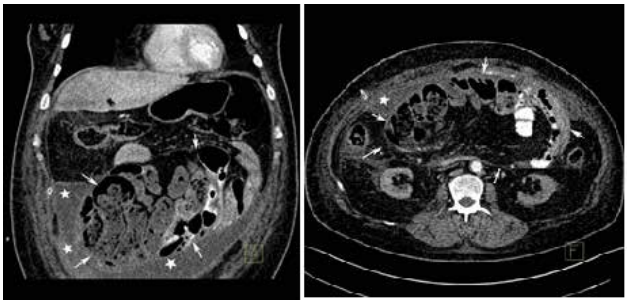

Figure 1a-b: Abdominal coronal (a) and axial (b) maximum intensity projection (MIP) CT images show small intestinal loops encased by a thin fibrous membrane and concentrated to a zone inside a cocoon-like structure (arrows). A fluid collection surrounding the sac is also visible (asterics). The colonic loops are seen outside the sac.

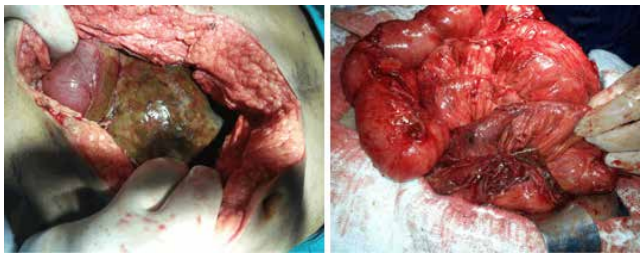

Figure 2a-b; During the operation all small intestinal segments as well as omentum were encased by a thick fibrous membrane (a). Omentum and intestinal loops freed after adhesiolysis (b) are seen.

Discussion

Abdominal cocoon or sclerosing encapsulating peritonitis is a rare condition that was first described by Foo et al. in 1978 [6]. It is characterized by intestinal obstruction and ileus as a result of encasement of small intestines totally or partially by a thick fibrous sac. It is classified as idiopathic and secondary. The former is seen in young women in tropical countries and subclinical peritonitis secondary to retrograde menstruation is considered responsible [7-10]. The secondary form, on the other hand, develops as a result of long term peritoneal dialysis [1,7,8], ventriculoperitoneal shunt [9], long term treatment with beta blockers [7,8], abdominal tuberculosis [10], abdominal surgery [7], liver transplantation [11], systemic lupus erythematosus, gastrointestinal malignancies, and protein S deficiency [12,13]. It has been suggested that the above mentioned conditions lead to fibrosis by causing peritoneal irritation and inflammation.

The clinical features of abdominal cocoon include abdominal pain, nausea, vomiting, weight loss, a non-tender palpable mass lesion, and signs and symptoms of intestinal obstruction. The laboratory findings are nonspecific and may include a mildly elevated white blood cells or C-reactive protein, hypoalbuminemia, and anemia [9].

Majority of cases are incidentally diagnosed during laparotomy performed against obstructive symptoms. A high degree of suspicion is required for preoperative diagnosis of abdominal cocoon syndrome [14]. Imaging modalities have an important role in the diagnosis; there are well-defined radiological clues that guide diagnostic process. On upright plain abdominal film air-fluid levels may be apparent or it may be totally normal. Barium studies demonstrate dilated, small intestinal loops in addition to a delayed transit time.

Ultrasonography shows dilated intestinal loops, free fluid, and, if thickened enough, a fibrotic membrane encasing intestinal loops. However, it may not be always possible to put the diagnosis with plain film and ultrasonography. CT is considered gold standard for diagnosis of ACS. The classical finding on a CT scan is presence of ascites between small intestinal loops swept to a side or the accumulation of small intestines at midline, which is encased by an envelope having soft-tissue density [9]. Other CT findings include ascites or loculated fluid collections, peritoneal thickening and contrast uptake, peritoneal calcification particularly in patients with end-stage renal disease, intestinal mural thickening, and tethering or fixation of bowel loops. Thanks to coronal and sagittal reformatted images, multidetector CT is superior to helical CT with respect to not only delineation of the disease extent and its indistinct radiologic findings, but also preoperative planning for surgery.

Surgical resection of the membrane and the adhesions is the best treatment option. Recently, cases successfully treated with laparoscopic technique have been reported [14,15]. In mildly symptomatic patients total parenteral nutrition and nasogastric decompression are the treatment modalities of choice. In addition to these, colchicine, corticosteroids, and immunosuppressive agents (mycophenolatemophetyl, azathioprine) may be used in mild disease. Lafrance et al. [15] successfully treated 2 cases with ACS secondary to peritoneal dialysis and Solak A and Solak I [3] one case with primary ACS with mycophenolatemophetyl and corticosteroid.

Our patient also underwent peritoneal dialysis for end-stage renal disease. Therefore, it was considered as a secondary ACS case. Abdominal cocoon syndrome is a rare and late complication of peritoneal dialysis. CAPD is one of the most common causes of secondary ACS. Our case is the first case in which CAPD-induced ACS was diagnosed and spontaneous perforation developed during follow-up. In fact, the possibility of free perforation appears unlikely because intestinal loops are encased by a fibrous membrane. We considered that perforation took place as a result of impaired microcirculation of intestinal loops. Abdominal cocoon syndrome is seen in approximately 1% of patients on CAPD therapy; its prevalence increases with longer treatment duration and at 8th year it may be present in 20% of patients [16]. Its etiology is not exactly known; however, a CAPD duration of more than a several years, type of the dialysate and episodes of bacterial and chemical peritonitis are risk factors for AC development [17,18]. Timely diagnosis and cessation of CAPD therapy may prevent disease progression and further complications. Nevertheless, abdominal cocoon syndrome may also rarely become manifest after cessation of CAPD. Management of the disease is challenging once it is progressed. Thus, renal replacement therapy may be scheduled at an early period to prevent ACS that may cause serious morbidity and mortality by early diagnosis since the disorder is irreversible. Despite some benefits of immunosuppressive therapy have been reported, acute complications such as small intestinal obstruction can only be managed with surgical technique [19].

Conclusion

Abdominal cocoon should be remembered in patients on CAPD therapy, especially when CAPD loses its functions after recurrent attacks of peritonitis. One should also be aware that clinical signs of peritonitis may not become evident in the case of intestinal perforation in patients with ACS. In such cases, CT has an important role in making the diagnosis.

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Journal of Surgery
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Case Report Open Access

Iatrogenic Abdominal Wall Defect from Chronic Evisceration of Intestine: A Complication of Fetal Vesico–amniotic Shunt

Dayang Anita Abdul Aziz[1*], **Marjmin Osman**[1], **Syarizlzry Sehat**[1], **Rohana Jaafar**[2] **and Zarina Abdul Latiff**[2]

[1]*Paediatric Surgery Unit, Department of Surgery, UKM Medical Centre, Malaysia*

[2]*Department of Pediatrics, UKM Medical Centre, Malaysia*

[*]**Corresponding author**: Dr. Dayang A Aziz, Associate Professor, Head of Pediatric Surgery UKM Medical Centre, Department of Surgery, Level 8, UKM Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras 56000, Kuala Lumpur, Malaysia, Tel: +6012 3059439; Fax: +603 91456648; E-mail: dayanganita@yahoo.co.uk

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Abstract

Vesico-amniotic shunt is one of the methods used to relieve fetal bladder obstruction in some cases of lower urinary tract obstruction. We highlight a 35 week gestation baby boy, who developed acquired abdominal wall defect following placement of the antenatal vesico-amniotic shunt. It is one of the rare complications of placement of vesico- amniotic shunt.

Keywords Fetal; Lower urinary tract obstruction; Abdominal wall defect

Introduction

Lower Urinary Tract Obstruction (LUTO) in fetus if left undiagnosed can lead to grave complications in newborn. With recent advancement in fetal management, LUTO can now be diagnosed antenatally. Creation of vesico-amniotic shunt is one of the treatments of choice. This procedure is not without complications.

Case Report

We highlight a male baby, born at 35 weeks of gestation via emergency LSCS who developed an unusual complication from a chronic dislodgement of catheter used for vesico-amniotic shunt procedure. Antenatally, at 19 weeks of gestation, the mother was noted to have oligohydromnios. Detail antenatal scan confirmed the finding and revealed that the fetus also had a left multicystic kidney and bilateral hydronephrosis. LUTO was diagnosed in the fetus and decision was made for fetal intervention; a vesico-amniotic shunt was performed at 22 weeks of gestation. The shunt-catheter was noted to dislodge from the fetal bladder at 31 week of gestation. The oligohydromnios recurred and the pregnancy was terminated at 35 weeks. At birth the baby required immediate ventilation with high setting. He was not dysmorphic. There was a noticeable 2×2 cm round defect at the abdomen, above and to the left of the umbilicus. Small bowel eviscerated through the defect together with the shunt catheter (Figure 1-3). The bowels were twisted and dusky. He was also diagnosed with possible urethral hypoplasia after episode of anuria. Only a tip of the urinary catheter was able to admit into the urethra. Urgent bedside surgical repair was performed and intraoperatively, a band was noted across the bowel causing narrowing of the bowel. The bowel was also twisted at the axis. The bowel improved in color after released of the band and untwisting of the bowel. The abdominal defect was closed in layers and suprapubic catheter inserted. Despite the surgical intervention, the baby succumbed to the complication of pulmonary hypoplasia at day 3 of life.

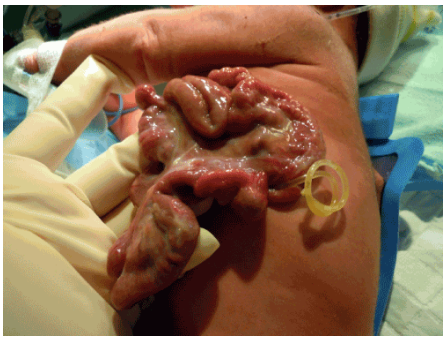

Figure 1: Matted and dusky bowel with visible vesicoamniotic catheter.

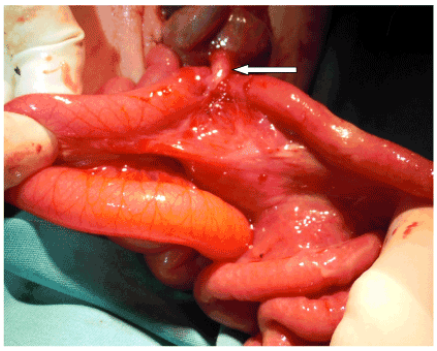

Figure 2: Arrow showing a band across the bowel where the volvulus occurred.

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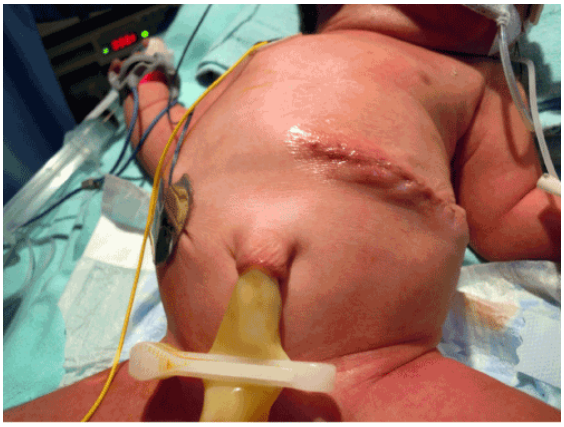

Figure 3: Bedside surgical closure performed.

Discussion

Severe oligohydromnios has complications detrimental to fetal life such as pulmonary hypoplasia and deformations of face and extremities. LUTO is known to cause severe oligohydromnios. In view of this, fetal intervention has gained popularity and one of the commonest interventions is vesico-amniotic shunting. Vesico-amniotic shunting as treatment for LUTO is indicated if patient fulfills the criteria. It will relieve the fetal bladder obstruction and restore amniotic fluid dynamic and volume. This will prevent oligohydromnios and ultimately prevent pulmonary hypoplasia.

Like any other intervention, this procedure is not without complications. Several theories were proposed previously to explain the formation of hernia. Placement of the shunt-catheter is usually put low in the bladder to avoid displacement. High placement will result in a defect in the puncture site when the bladder returns to pelvis after decompression [1]. Furthermore as the fetus grows in size, the defect will expand as well. In some cases, the herniation occurs as a result of increase intra-abdominal wall pressure or multiple puncture sites of the catheter. The most common complication reported was shunt migration and dislodged (20–60%) followed by shunt occlusion (10-25%), chorioamnionitis, preterm labour and miscarriage (1-2%). Bowel and bladder herniation have also been reported [2-4].

In our patient, the placement site was unusual and had resulted in iatrogenic abdominal wall defect with chronic evisceration of the small bowel. Despite the known complications from vesicoamniotic shunt procedure, the risk are well worth taking in view of the outcome of the fetus in general –unfortunately not so in our patient. Thus, selection criteria should be refined. Bedside intervention was essential in our case as the bowel was twisted and the baby was not able to be transferred to the operating theatre as he was on high setting ventilation.

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Journal of Surgery
[Jurnalul de Chirurgie]

Case Report Open Access

Ewing's Sarcoma of the Sternum: A Case Report and Literature Review

Ahmed Dehal[1*], Hannah Copeland[2], Albert Kheradpour[2], Mark Martin[2], Jason Wallen[2] and Salman Zaheer[2]

[1]*Kaiser Permanente, Fontana, CA, USA*

[2]*Loma Linda University Medical Center, Loma Linda, CA, USA*

[*]**Corresponding author:** Ahmed Dehal, MD, MPH, Department of General Surgery, Kaiser ermanente, Fontana, CA, USA, Tel: (909)247-5626; Fax: (909)247-4626; E-mail: ahmed.dehal@gmail.com

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Abstract

A 16 year old male presented with Ewing's sarcoma of the sternum which extended into the anterior mediastinum. At presentation, there was no evidence of metastatic disease. The patient was initially treated with chemotherapy. The residual tumor was subsequently resected and the sternal defect was repaired with a polyprolene mesh and a muscle flap. Post-operatively, the patient did well and was discharged home. The patient has been seen in the clinic and is doing well post-operatively. Although extremely rare, Ewing's sarcoma occurs in the sternum. A combined effort between oncology, thoracic surgery and plastic surgery for single excision and reconstruction is optimal for the patient.

Keywords: Ewing; Sarcoma; Sternum; Case; Report

Introduction

Ewing sarcoma is a solid tumor of bone and soft tissue can arise in any bone of the body. However, the most common sites of disease include the pelvis, ribs, and long-bones of the extremities. Ewing's sarcoma of the sternum has been rarely reported in the literature. Most neoplasms of the sternum are metastases. Primary tumors are relatively uncommon in this site; however, primary tumors of the sternum are much more frequently malignant than benign. Whether it is believed to be primary or secondary, a new mass in the sternum should be considered malignant until proven otherwise [1].

These tumors are most often found in children (median age, 16 years). They manifest clinically as painful masses. Metastases to lung, bone, and lymph nodes are seen in approximately 70% of patients with Ewing sarcoma. Overall 5-year and 10-year survival is only approximately 50%, and the outcome is ultimately determined by the presence of metastasis. Survival after resection is also dependent on the histology and grade of the tumor [2].

Since the tumor was first described more than half a century ago, the subject has been marked by controversy and uncertainty, and approaches to therapy have varied widely. The treatment of Ewing sarcoma relies on a multidisciplinary approach, coupling highly intensive chemotherapy with surgery, and/or radiotherapy. We report a case of a Ewing's sarcoma of the sternum that was treated with chemotherapy and surgery.

Case Report

A 16 year old male had an enlarging chest wall mass, tenderness and a 30 lb weight loss. The patient denied any chest pain or shortness of breath. The child was an otherwise healthy with no history of other medical problems. Computed Tomography (CT) scan of the chest showed anterior sternum calcified mass extending into the anterior mediastinum (Figure 1). The mass was biopsied and found to be Ewing's sarcoma. The patient was treated with 12 cycles of chemotherapy (vincristine, cyclophosamide, and topotecan). The tumor decreased in size by two-thirds its original size. Five months later the tumor was excised in a circumferential fashion with 1.5 cm negative margins (Figure 2). One third of the sternum was removed along with adjacent intercostal muscles and rib ends. The plastic surgery team placed alloderm over the heart, polyprolene mesh, mobilized a left lattisimus dorsi muscle flap and tunneled it under the left chest over the sternal space. Three sternal plates were placed across the sternum. Post-operatively, the patient did well and was discharged to home on post-operative day 10. The patient has been seen in the clinic and is doing well post-operatively (Figure 3). He is now one year after diagnosis and he is in good health with no evidence of recurrent tumor.

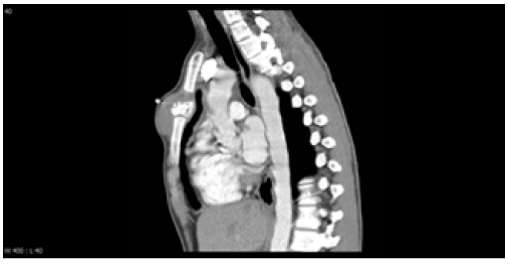

Figure 1: CT scan of the chest showing the sarcoma of the sternum.

Discussion

Primary Ewing's sarcoma of the sternum is extremely rare. Only a few studies have reported on Ewing's sarcoma of the sternum, and nearly all of them had small patient populations. A literature search revealed only four reported cases of primary Ewing's sarcoma of the sternum [3-6]. However, no clinical data were available for three of those cases. Ewing's sarcoma of the sternum has not been recorded in the Intergroup Ewing's Sarcoma Study [7]. It was also not noted in

several old series ranging from 12 to 73 cases (totaling 537 cases) of this cancer [8-17].

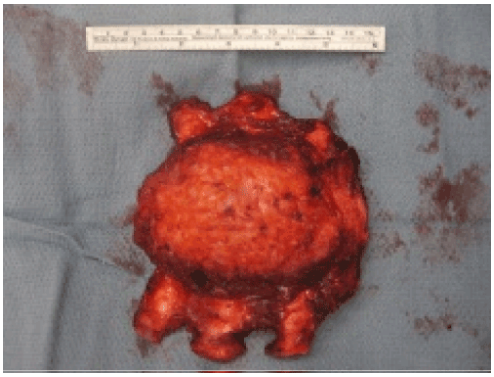

Figure 2: Resected sarcoma specimen.

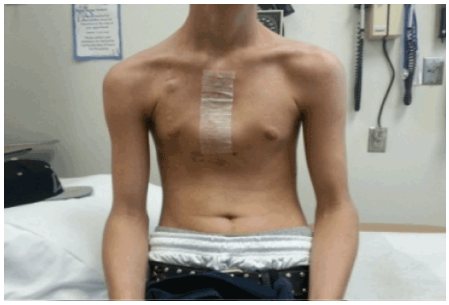

Figure 3: Postoperative wound.

The first case was reported in a 12 years old female who was successfully treated with chemotherapy and radiation followed by surgery [3]. The second case was found in a series of 107 cases from Tara Memorial Hospital in Bombay, India [4]. The third case was reported in a large study of 11,087 bone tumors in the Dahlin tumor series at the Mayo Clinic. In their study, only 66 (0.6%) were primary malignant tumors of the sternum. Among those, only 66 were primary sternal malignancies including 22 chondrosarcomas (33%), 20 myelomas (including plasmacytomas) (30%), 14 lymphomas (21%), eight osteosarcomas (12%), one fibrosarcoma (1.5%), and one Ewing sarcoma (1.5%) [5]. The last case was reported in the most recent report from Memorial Sloan Kettering Cancer Center describing their experience with primary and secondary malignancies of the sternum over 69-year period (1930 to 1999). In their series of 58 patients with primary sternal malignancies were identified. Among this, there were 28 chondrosarcomas (48%), 11 osteosarcomas (19%), nine plasmacytomas (15.5%), six lymphomas (10%), one fibrosarcoma (1.7%), one angiosarcoma (1.7%), one malignant fibrous histiocytoma (1.7%), and one Ewing sarcoma (1.7%), [6].

Tumors of the sternum have been considered a challenging problem for a long time. Stability and reconstruction of chest wall defects have caused the main difficulties in radical full-thickness resections. Improvement of surgical techniques, especially by means of myocutaneous flaps and prosthetic materials, has resulted in successful sternectomies and simultaneous reconstructions. Incarbone et al in their series of 52 patients who underwent sternal resection for primary and secondary tumor concluded that extensive resection of the sternum for primary or secondary tumors followed by reconstruction with prosthetic material or a myocutaneous flap is a safe and effective treatment [18].

Multimodal approaches within clinical trials, employing combination chemotherapy and surgery and/or radiotherapy, have raised 5-year survival rates from <10% to >60%. The current recommendations by the European Society for Medical Oncology Group consider complete surgery, where feasible, as the best modality of local control. Radiotherapy should be applied only if complete surgery is impossible, and should be discussed where histological response in the surgical specimen is poor (i.e. >10% viable tumor cells) [19].

All current trials employ three to six cycles of initial chemotherapy after biopsy, followed by local therapy and another six to ten cycles of chemotherapy usually applied at 3-week intervals. Treatment duration is thus 8–12 months. Agents considered most active include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin and etoposide. Virtually all active protocols are based on four- to six-drug combinations of these substances. According to findings from the European Intergroup Cooperative Ewing's Sarcoma Study, protocols that have proved to be most effective include at least one alkylating agent (ifosfamide or cyclophosphamide) and doxorubicin [20].

In a large series of adult Ewing sarcoma patients from the Mayo Clinic, outcomes were analyzed for 102 patients. The authors reported improved results in the modern portion of their study (1993 through 2007 versus 1977 through 1992) reflecting a move toward using surgery along with etoposide and ifosfamide-based chemotherapy. The authors reported a five-year overall survival rate of 73% and a five-year event free survival rate of 60% in their modern group. Furthermore, local failure was 18% in the surgery group, compared with 33% in the radiation group and 0% with the combination of the two local modalities [21].

Tumor resection of Ewing's sarcoma in the sternum can be performed without mutilation. Our patient has only a mild cosmetic defect. Bony resection has a particular advantage in the sternum, where long-term surgical morbidity is small. Thus, neoadjuvant chemotherapy followed by excision in this site should certainly be considered. We presented a case of Ewing's sarcoma of the sternum in a 16 years old male who was successfully treated with chemotherapy and surgery. A combined effort between oncology, thoracic surgery and plastic surgery for single excision and reconstruction is optimal for the patient.

Acknowledgement

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Conflict of Interest Statement: The authors indicate no potential conflict of interest or financial ties.

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Case Report Open Access

Esophageal Perforation after Thoracic Vertebral Fracture in an Ankylosed Spine: Case Report and Review of the Literature

Johanne Summers[1*], **Craig Timms**[1] **and Tony Goldschlagera**[2]

[1]*Department of Neurosurgery, Monash Medical Centre, 3168 Victoria, Australia*

[2]*Department of Surgery, Monash University, 3800 Victoria, Australia*

[*]**Corresponding author**: Dr. Johanne Summers, Department of Neurosurgery, Monash Medical Centre, 3168 Victoria, Australia, Tel: (+61) 402579639; Fax: (+61) 3 95926962; E-mail: **johannesummers@gmail.com**

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Abstract

We present the case of a 74 year-old male with delayed diagnosis of post-traumatic thoracic esophageal perforation that occurred secondary to thoracic vertebral fracture in an ankylosed spine. The injury resulted after a fall from chair secondary to an unconscious collapse due to Ventricular Fibrillation (VF). At 8 days after the injury, the patient was diagnosed with esophageal perforation, secondary to fourth thoracic vertebral fracture without neurological deficit. The esophageal laceration was complicated by sepsis with bacteremia, pleural empyema and mediastinal abscess. Non-surgical management for the esophageal perforation, chest complications and thoracic spine fracture resulted in complete recovery. A case report and review of the literature is presented. We report the first case of post-traumatic thoracic esophageal perforation secondary to thoracic T4 vertebral fracture, in a patient with an ankylosed spine that survived neurologically intact after successful conservative management.

Keywords: Esophageal Perforation; Thoracic Esophageal Injuries; Thoracic Vertebral Fracture; Ankylosed Spine; Conservative Management.

Introduction

Esophageal perforation is a life threatening injury, with serious complications such as sepsis and mediastinitis, and mortality rates 18% to 48% [1-6]. Mortality rates greater than 50% are reported with delayed diagnosis and treatment after 24 hours [7-9]. Prevention of serious complications revolves around early diagnosis and treatment [4,5]. The causes of esophageal injuries include iatrogenic, penetrating (20-25%) and blunt trauma (<10%). Blunt spinal injury as a cause of esophageal perforation is uncommon, and most of the reported cases are due to cervical spine pathology [10-14]. Thoracic spinal fracture resulting in thoracic esophageal perforation is extremely rare, with an incidence of less than 0.2% [15] and there are only a few reported cases in the literature [7,16-20]. It can occur when thoracic vertebral fracture causes posterior esophageal wall laceration and typically results in death or severe morbidity [1-3,6,8,21,22]. A case report and review of the literature is presented. We report the first case of post-traumatic thoracic esophageal perforation secondary to thoracic T4 vertebral fracture after a low velocity fall, in a patient with an ankylosed spine that survived neurologically intact, successfully treated with conservative non-surgical management.

Case Report

A 74 year-old man, independent from home, was admitted to our hospital after a fall from a chair onto his back, following an episode of VF resulting in an unconscious collapse. After appropriate Automatic Internal Cardiac Defibrillator (AICD) discharge for VF (defibrillator activated, shocked back to paced rhythm), the patient awoke complaining of central chest pain radiating to his back. On arrival of the ambulance service, the patient had a Glasgow Comma Score of 15 and stable hemodynamics, he was neurologically intact and afebrile. On admission to the hospital emergency department, the patient was febrile at 40°C, but remained stable without neurologic deficit, denied chest or spine tenderness, and there were no symptoms or signs indicating spinal cord compromise. The patient's past medical history consisted of atrial fibrillation on warfarin, dilated cardiomyopathy with an AICD, osteoarthritis, ankylosing spondylitis, renal stent, hypertension, gout, peripheral vascular disease, glaucoma and a past smoking history.

Management and investigation were instigated for the initial diagnosis of unconscious collapse associated with the VF event, which was presumed secondary to sepsis. Initial thoracic spine imaging was not performed. The patient continued to have high fevers with chills and rigors. Blood cultures were positive for staph hominis, strep mitus, and strep milleri bacteremia, treated with intravenous antibiotics, as directed by the infectious diseases unit. The initial source of the sepsis was presumed urinary tract source, as the patient had a complicated renal stent insertion one month prior to admission. From the time of injury the patient complained of chest pain radiating to the inter-scapular region, but did not report swallowing problems. The patient was mobilized on day 3 with physiotherapy.

Despite antibiotic therapy the patient had persistent fever, raised inflammatory markers, and ongoing chest and back pain, prompting further investigation. On day 8 after injury, the patient underwent a chest Computed Tomography (CT) scan, which revealed thoracic esophageal perforation secondary to fourth thoracic vertebral fracture, complicated by pleural empyema and mediastinal abscess. There was a moderate amount of free posterior mediastinal gas anterior to the thoracic spine and on the right side of the mediastinum, with a rind of soft tissue but no visible fluid. Oblique fracture of the T4 vertebral body extending from anterosuperior to posteroinferior with 4mm of retrolisthesis, no involvement of the pedicles or posterior elements, and underlying ankylosed spine with extensive syndesmophyte (Figure

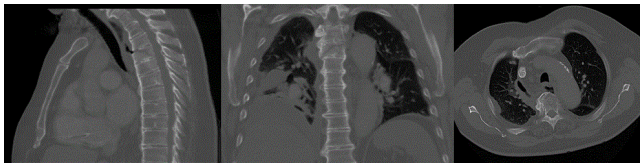

Figure 1: Sagittal, Coronal and Axial CT scans - Oblique fracture T4 vertebral body, free mediastinal gas. Posterior to esophagus at T4 level.

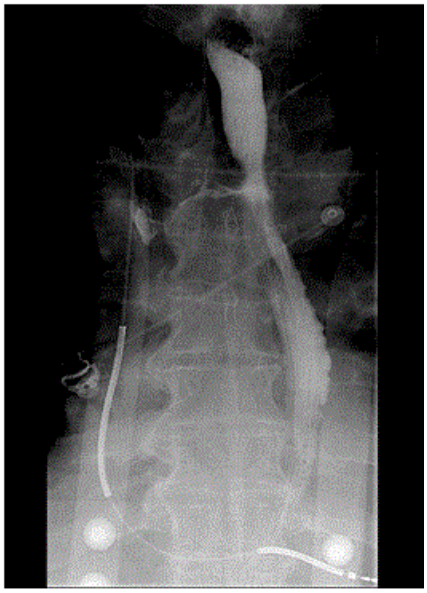

Figure 2: Gastrograffin swallow Esophagography. Contrast extravasation at the T4 level.

1). In addition, there was evidence of right lung middle and lower lobe consolidation with pleural effusion. Diagnostic imaging with MRI was contraindicated due to the patient's AICD. Gastrograffin swallow contrast esophagography confirmed esophageal laceration and ongoing leak at the level of the T4 vertebral body, with active contrast extravasation from the esophagus to the right side of the mediastinum (Figure 2).

The esophageal perforation, sepsis, chest complications and thoracic spine fracture were successfully treated with non-surgical management. The Gastroenterologist advised conservative management for the traumatic esophageal laceration and stenting was not employed due to the delayed diagnosis and established infected pleural and mediastinal complications. Cardiothoracics instigated conservative management for the pleural empyema and mediastinal abscess, and the Infectious diseases unit directed intravenous antibiotic therapy. The patient was treated nil by mouth, with total parenteral nutrition, and followed with serial gastrograffin swallow studies. Non-surgical management was directed by Neurosurgery for the thoracic vertebral body fracture. This decision was made as the patient had already been mobilized, and follow-up imaging showed no change in fracture alignment, as well as the patient's significant comorbidities, in which precluded a general anesthetic in the prone position. Initial orthotic spinal brace fitting was contraindicated due to chest compromise.

The patient was nursed with spinal precautions and log roll pressure care, until the esophageal leak and chest complications had resolved. The patient was managed in the intensive care unit for 4 days, and then nursed in a single room on the general ward. At day 42 after injury, gastrograffin swallow study showed the esophageal laceration had resolved, with no evidence of extra-luminal contrast extravasation to suggest ongoing leak. A repeat chest CT scan revealed resolution of the chest collections/empyema and mediastinal gas, and stable configuration of the T4 vertebral fracture with evidence of early bone healing. Diet was restarted without complications. The esophageal laceration healed without further leak, and the patient tolerated oral intake without swallowing difficulties. The patient was mobilized in a Boston brace custom-made overlap "clam shell" design (anterior and posterior sections, side fastenings and shoulder straps), and discharged to a rehabilitation facility. The thoracic fracture remained stable on serial spine imaging and CT scan showed fracture union. The patient remained neurologically intact, and conservative non-surgical management resulted in complete recovery.

Table I: Cases of post-traumatic esophageal perforation after thoracic spine fracture; MA – Motorcycle Accident; MVA – Motor Vehicle Accident; F – Fall; AS – Ankylosed Spine; E – Esophagus; TS – Thoracic Spine; Ch – Chest; C – Conservative; S – Surgery.

CASE (Reference)	LEVEL	CONTRIBUTING FACTORS	DELAYED DIAGNOSIS [Time]	MANAGEMENT	NEUROLOGICALLY INTACT	SURVIVED
1 (16)	T3, T4	MA	Yes [14 Days]	E: [C] TS: [S] Ch: [S]	Yes	Yes
2 (7)	T3, T4	MA	Yes [11 Days]	E: [C] TS: [C] Ch: [C]	Yes	No
3 (17)	T3, T4	MA	No	E: [S] TS: [S]	No	Yes

				Ch: [S]		
4 (18)	T3, T4	MVA	Yes [6 Days]	E: [S] TS: [S] Ch: [C]	Yes	Yes
5 (19)	T2	MVA	Yes [5 Months]	E: [C] TS: [C] Ch: [C]	No	Yes
6 (20)	T3, T4	MVA	No	E: [S] TS: [S] Ch: [S]	No	Yes
7 (Current)	T4	F, AS	Yes [8 Days]	E: [C] TS: [C] Ch: [C]	Yes	Yes

Discussion

Esophageal perforation is rare and is associated with high morbidity and mortality [1-3,6,8,21,22]. It can be attributed to a number of etiologies, including spontaneous rupture, iatrogenic injury, blunt or penetrating trauma [2]. In 15 to 20% of esophageal perforations trauma is the cause, often due to penetrating neck or thorax injury, and more common with cervical spine trauma [10-14]. Blunt trauma can occur in deceleration injury, with raised intraluminal pressure resulting in esophageal wall tear.15 Forced neck hyperextension can cause cervical esophageal perforation, and shearing-distraction injuries can result in thoracic esophageal perforation [16]. Delayed diagnosis and treatment can be due to lack of obvious symptoms or signs masked by other injuries, and result in serious complications such as sepsis, pleural empyema and mediastinitis [7,23]. Presentation can include a range of symptoms, dysphagia, odynophagia, dyspnea, progressive sepsis, tachycardia, pyrexia, chest pain and surgical emphysema. Prompt diagnosis and management is important to prevent life threatening complications, with greater than 50% mortality rates reported for surgery more than 24 hours after esophageal perforation [7-9]. In certain cases, non-surgical management can be employed [2,3,24].

In the largest comprehensive review to date of thoracic esophageal perforations there were no cases of thoracic spine fracture etiology [25]. There are only six reported cases of post-traumatic thoracic esophageal perforation due to thoracic spine fractures (Table 1) [7,16-20]. We present the first case not associated with a road traffic accident, in a patient with an ankylosed spine, with injury sustained after a low velocity fall. This is the only reported case of post-traumatic thoracic esophageal perforation secondary to thoracic T4 vertebral fracture, in a patient with an ankylosed spine that survived neurologically intact after successful conservative management.

The spinal column is located close to the esophagus between C5 and T4 [7]. with the physiologically narrow esophageal region close to the third and fourth thoracic vertebrae [8]. With hyperextension injury of the spine, forces can be transferred from the spine to the esophagus is this area, resulting in esophagus perforation [7]. Penetration of the esophagus can result from a spinal fracture fragment [16]. Contrast esophagography is the gold standard for localization and diagnosis of esophageal perforation [2,3,15]. Extra-luminal peri-esophageal air is reported as the most useful finding on chest CT [26]. Chest CT can also identify thickening of the esophageal wall, esophageal distortion or displacement at the cervico-thoracic junction, and para-esophageal manifestations such as mediastinal abscess, and pleural collections or effusions [2,26-28].

The presented case highlights the importance of vigilance in all trauma cases involving patients with ankylosing spinal enthesopathy, even after a low velocity mechanism. This report also serves to increase clinician awareness of possible thoracic esophageal injury following upper thoracic spine fracture. Ankylosing Spondilitis (AS), also known as Marie-Strümpell disease, is a seronegative arthropathy, with peak incidence age 17 to 35 years. The primary skeletal site involved is the spine, usually progressing rostrally from the sacroiliac joints and lumbar spine. The spinal enthesopathy produces the “bamboo spine”, square-appearing osteoperotic vertebral bodies with bridging syndesmophytes due to ossified ligaments and calcified intervertebral discs. The rigid spine of AS when fractured acts as a long lever, and fracture may occur following minimal trauma, these fractures are typically very unstable and usually required surgical fixation. In this case it was fortunate that the fracture was stable and able to withstand early mobilization.

Esophageal injuries can be managed with conservative management or operative intervention, with supportive measures to control sepsis and provide adequate nutrition [2,3]. Surgical options may include primary closure, drainage, diversion, or esophagectomy [2,3]. In selected cases, esophageal perforations can heal with non-operative management consisting of broad-spectrum antibiotics, strict oral hygiene, nil orally and total parental nutrition [2,3]. The complex decision on treatment for the esophageal perforation depends on the patient’s clinical circumstances. Treatment selection should be based on patient condition and performance status, timing of diagnosis, resources available, esophageal pathology, and presence/absence of complications, local phlegmon, and/or sepsis [25]. Prompt diagnosis and management of esophageal perforation is of paramount importance to attempt to avoid serious complications. Our case report

demonstrates that good outcome can be achieved with non-operative management.

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Bolnav cu Gist Gastric Gigant; Supraviețuire Nesperată Prezentare de Caz

M Gheorghe[1], **D Predescu**[1], **N Copca**[2], **Cristina Iosif**[3], **F Băcanu**[4] **and S Constantinoiu**[1]

[1]*Clinica de Chirurgie Generală și Esofagiană, Spitalul Clinic Sfânta Maria București, Universitatea de Medicină și Farmacie Carol Davila" București, Romania*

[2]*Centrul de Cercetare Chirurgie, Spitalul Clinic Sfânta Maria București, Universitatea de Medicină și Farmacie Carol Davila" București, Romania*

[3]*Departamentul de Anatomie Patologică, Spitalul Clinic Sfânta Maria București, Universitatea de Medicină și Farmacie Carol Davila" București, Romania*

[4]*Departamentul de Oncologie, Spitalul Clinic Sfânta Maria București, Universitatea de Medicină și Farmacie Carol Davila" București, Romania*

[*]**Correspondence author:** Mircea Gheorghe, MD, Department of General and Esophagian Surgery, "St. Mary" Hospital București, Bd. Ion Mihalache, No 37-39, Sector 1, București, Romania, Tel: +40 (0) 721 22 60 20; Fax: 0040721226020; E-mail: rgheorghemircea@yahoo.com

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Abstract

Background: Gastrointestinal Stromal Tumors (GIST) are rare neoplasms, with sever prognosis in advanced cases. Until the discovery of Tyrosin Kinase Inhibitors (TKI), the life expectancy was very poor for patient with metastatic tumors, postoperative relapses or unresectable disease. Introduction of TKI therapy provided an unexpected survival rate, controlling the disease with very good tolerance.

Method: We present a case report representative for GIST pathology. It is the first case of our GIST series of patients, operated in General and Esophageal Surgery Clinic of "St. Mary" Hospital Bucharest. A multidisciplinary approach and a complex, multimodal, surgical and oncological treatment was applied, with good response confirmed by the long-term follow-up. A 79 years old patient was diagnosed in 2004 (at the age of 70 years) with giant gastric GIST. He underwent a total gastrectomy, splenectomy and left pancreatectomy; the resection was considered as R1 because the tumor capsule was not complete. The adjuvant treatment with TKI was started postoperatively for 2 years. The recurrence was noted one year after the adjuvant therapy stop. Then the TKI treatment was restarted with very good tolerance and control of disease at 9 years.

Conclusion: The TKI therapy allows long-term control of the malignant GISTs in term of overall survival and quality of life, even when the surgical procedure is not optimal.

Keywords: Gastro-Intestinal Stromal Tumors; Malignant; Gastric Gist; Gastrectomy; Tyrosin Kinase Inhibitot; Imatinib Mesylate; Survival

Introducere

Tumorile stromale gastrointestinale (Gastro-Intestinal Stromal Tumors - GIST), sunt descoperiri rare, cu un prognostic sever în cazurile avansate. Până la descoperirea inhibitorilor de tirozin kinază (ITK), pentru pacienții cu tumori metastatice, cu recidive postoperatorii precum și cu tumori nerezecabile, speranța de viață era foarte redusă. Introducerea ITK (de ex. Imatinib mesilat) a permis controlul bolii și prelungirea nesperată a supraviețuirii [1].

În lucrarea de față prezentăm primul pacient cu GIST gastric operat în clinică, un caz particular prin faptul că a prezentat o tumora gigantă gastrică ce a necesitat un abord multidiciplinar și un tratament complex, chirurgical și oncologic, care i-au asigurat o supraviețuire nesperată de 9 ani de la momentul diagnosticului.

Prezentare De Caz

Pacient de 70 de ani, obez, (indice de masă corporală (IMC) de 34,8 kg/m^2), hipertensiv, se prezintă în noiembrie 2004 pentru disconfort epigastric, scăderea apetitului alimentar, scădere în greutate de circa 5 kg în ultimele 2 luni și astenie fizică.

Examenul clinic identifică la nivel abdominal o formațiune tumorală palpabilă în epigastru. Examenele de laborator la internare au fost în limite relativ normale.

Endoscopia digestivă evidențiază o ulcerație gastrică localizată pe marea curbură gastrică; biopsiile au fost neconcludente.

Computer tomografia abdomino-pelvină confirmă prezența în etajul supramezocolic a unei formațiuni tumorale voluminoase, cu structură neomogenă, a cărei apartenență de organ nu poate fi precizată, cu compresia organelor cavitare din jur: stomac, colon transvers și invazia pancreasului și a hilului splenic. Nu se constată determinări secundare hepatice, sau limfoganglionare vizibile tomografic.

Se intervine chirurgical și se constată: tumoră gigantă gastrică, cu invazia pancreasului corporeo-caudal și a splinei. Se practică gastrectomie totală, pancreatectomie corporeo-caudală, splenectomie și refacerea continuității digestive prin anastomoză eso-jejunală pe ansă în "Ω". Rezecția a fost apreciata R1 deoarece, datorită volumului tumoral, în cursul mobilizării tumorale se descriu câteva mici efracții ale capsulei tumorale (Figure 1).

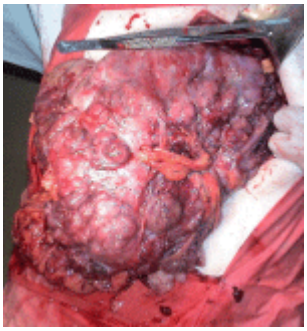

Figure 1: Formațiunea tumorală; aspect intraoperator.

Examenul histopatologic al piesei operatorii confirmă prezența unei tumori de 29 x 20 cm cu zone de necroză, ce înglobează corpul gastric și corpul pancreasului; sunt confirmate efracțiile de la nivelul capsulei. Microscopia (Figure 2) confirmă prezența celulelor de tip "spindle-cell" care, imunohistochimic, exprimă CD-117 (c-Kit) (Figure 3) și CD-34. Analiza mutațională evidențiază deleție la nivelul exonului 11.

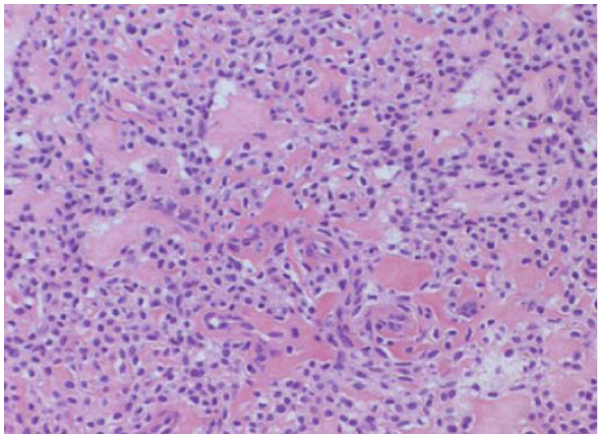

Figure 2: Microscopie (HE 10x): tumoră cu cellule de tip "spindle cell".

Prin utilizarea criteriilor histologice de stratificare a riscului de progresie a bolii, sediul tumorii, dimensiunea tumorală și numărul de mitoze identificate prin examenul anatomopatologic tumora este apreciată ca GIST cu grad ridicat al riscului de recidivă (>86%) și pacientul este inclus într-un proiect de cercetare al CECOG (*Central European Cooperative Oncology Group*) și primește Imatinib mesilat timp de 2 ani, fiind urmărit clinico-paraclinic pe întreaga perioadă a trialului clinic.

Urmarirea periodică prin examen CT nu evidențiază urme de recidivă intra-abdominală sau metastaze hepatice.

După părăsirea programului amintit, la 1 an de la întreruperea tratamentului, pacientul revine în clinică pentru controlul periodic și prezintă două recidive intra-abdominale, una dintre ele palpabilă la nivel paraombilical stâng, formațiuni evidente la computer tomografie (CT) și confirmate prin examen PET-CT FDG (Figure 4).

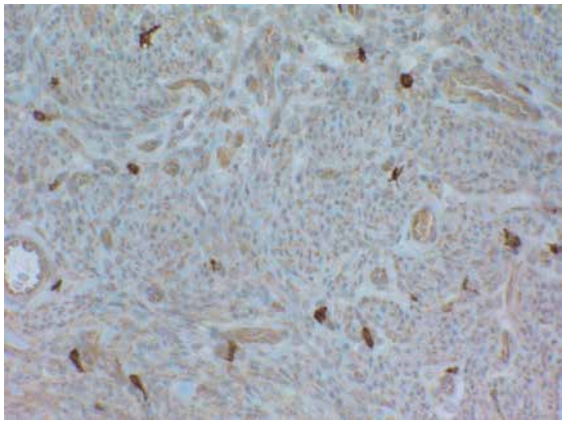

Figure 3: Imunihistochimie: celule positive la markajul CD-117.

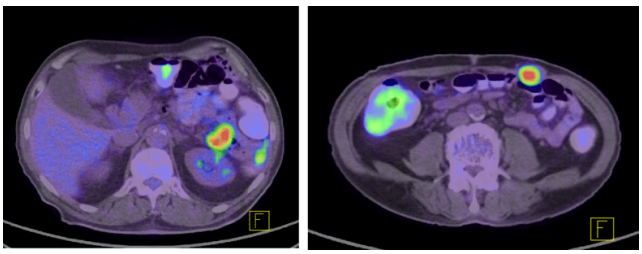

Figure 4: PET-CT: recidive abdominale cu localizare intraabdominală și parietală.

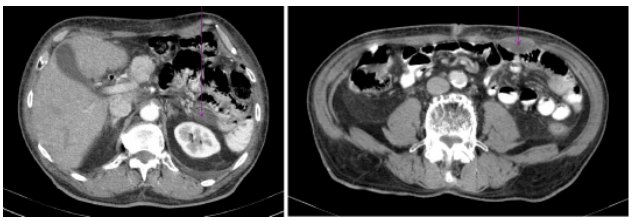

Figure 5: Examen CT: aspect stabil al recidivelor abdominale în cursul tratamentului cu ITK.

Pacientul reîncepe tratamentul cu Imatinib mesilat, 400mg/zi, iar controalele efectuate la un interval de 3 luni demonstrează un bun răspuns cu reducerea dimensiunilor tumorale, precum și o bună toleranță la tratament (Figure 5).

La ultimul control din octombrie 2013 pacientul este asimptomatic la nivel abdominal, fără nicio dificultate în efectuarea activităților zilnice și fără efecte secundare ale chimioterapiei.

Discuții

GIST reprezintă o forma rară de sarcom care ia naștere din celulele intersițiale Cajal sau din celulele stem nediferențiate, localizate în tunica musculară a tractului gastrointestinal. GIST poate afecta orice segment de tub digestiv dar apare cu predilecție la nivelul stomacului

60%, intestinului subțire 30%, duodenului 4-5%, rectului 4%, colonului și apendicelui 1-2% esofagului < 1%. [1] Foarte rar au fost descrise și GIST-uri extragastrointestinale [2]. Incidența a fost estimata la 1.5/100000 pe an [3].

Din punct de vedere imunohistochimic majoritatea GIST sunt pozitive pentru antigenul c-Kit (CD-117), DOG1, CD-34 și PCKθ. Majoritatea GIST prezintă mutații genetice la nivelul genelor pentru receptorii KIT și PDGFR, ce au ca rezultat proliferarea tumorală dar în același timp oferă ținte moleculare specifice pentru tratamente de tip ITK. Pentru GIST localizate tratamentul principal este cel chirurgical.

În ciuda eficacității tratamentelor, supraviețuirea pe termen lung nu este satisfăcătoare pentru toți pacienții, datorită pe de o parte rezistenței la tratament, primare sau secundare, sau pe de altă parte, efectelor adverse ce determină o slabă complianță la tratament.

Mai multe criterii au fost selectate și corelate cu prognosticul și supraviețuirea: localizarea tumorală, mărimea tumorii, activitatea mitotică, necroza tumorală, procentul de celule proliferative, caracterul invaziv, prezența simptomelor, tipul histologic, profilul imunohistochimic, prezența metastazelor sau rezecția R0 fără efracția capsulei tumorale. Miettinen și colab. [1] propun ca factori predictivi ai progresiei tumorale: localizarea, diametrul tumorii și numarul de mitoze și stratifică riscul de recidivă în patru grade (Table 1).

pacienții cu exon 9 mutat, întâlnit la cei cu localizare intestinală sunt mai puțin sensibili, doza necesară fiind dublă [7], fapt demonstrat și de evoluția cazului prezentat care avea o deleție l anivelul exonului 11 și a răspuns la tratamentul cu imatinib.

Table I: Factori prognostici pentru GIST.

Categorie de risc	Mărime tumorală (cm)	Nr de mitoze/50 HPF	Sediu tumoral	Risc de recădere %
Foarte scăzut	< 2	≤ 5	oricare	0
Scăzut	2-5	≤ 5	oricare	1,9-4,3
	5-10	≤ 5	stomac	9,6
	< 2	> 5	stomac	0
Intermediar	> 10	≤ 5	stomac	12
	2-5	> 5	stomac	16
	5-10	≤ 5	intestin	24
Înalt	>10	≤ 5	intestin	52
	< 2	> 5	intestin	50
	2-5	> 5	intestin	73
	5-10	> 5	oricare	55-85
	> 10	> 5	oricare	86-90

Berzi și colab. [4] afirmă după analiza a 158 de cazuri că doar 12% dintre pacienții cu mitoze >10/50 HPF (high power fields) rămân vindecați (disease free) după chirurgie, în timp ce toți pacienții cu mitoze >20/50 HPF prezintă recurența bolii. Ei argumentează că dacă numărul de mitoze și mărimea tumorală situează cazul în grupul de risc înalt, atunci numărul de mitoze devine variabila mai precisă.

Stratificarea riscului include și alți factori independenți cum ar fi: statusul marginilor de rezecție, ruptura tumorală sau statusul mutațional. Ruptura tumorală pre sau intraoperatorie este un factor de prognostic negativ care depășește ceilalți parametri amintiți, situând pacientul în clasa de risc foarte înalt, fapt demonstrat și de evoluția cazului nostru, în timp ce statusul mutațional nu a fost încă introdus în nicio clasificare de risc deși anumite genotipuri de GIST au un comportament patologic specific.

Imatinib mesilatul este primul tratament eficace în GIST. Este indicat ca tratament standard pentru GIST nerezecabil sau metastatic și de asemenea, pentru GIST operat, cu risc moderat sau înalt de recidivă sau pentru pacienții cu recidive postoperatorii ce nu mai sunt candidați la tratamentul chirurgical [5].

Imatinib mesilat acționează prin blocarea activării intracelulare produse de receptorii Kit sau PDGFRA, blocând legarea acestora de ATP și prevenind declanșarea semnalelor de creștere celulară, ceea ce oprește progresia bolii. Răspunsul la tratament este legat de tipul mutației la nivelul exonului c-Kit. Pacienții cu mutații la nivelul exonului 11 sunt mai sensibili la imatinib 400mg/zi [6], în timp ce

Tratamentul trebuie asigurat pe o durată nedeterminată, întreruperea fiind urmată relativ rapid de progresie tumorală în aproape toate cazurile considerate cu risc înalt [8].

În ultima perioadă numeroase lucrări subliniază rolul predictiv al mutațiilor genetice din GIST privind recurența bolii. S-au identificat mutații specifice ale exonului 11 asociate cu rata ridicată de metastazare și prognostic slab. Câteva lucrări subliniază că pacienții cu deleții la nivelul exonului 11, au probabilitate mai mare de a prezenta recurențe sau metastaze decât cei cu substituții sau duplicații la acest nivel [9,10]. Aceste date sunt în concordanță cu observația prezentată. Analiza mutațională ar putea deci oferi un algoritm de identificare a pacienților ce necesită pe de o parte o monitorizare mai atentă pentru a identifica recurența bolii dar și un tratament adjuvant pentru a preveni recurențele. De altfel, ultimele conferințe de consens recomandă utilizarea analizei mutaționale pentru o caracterizare mai precisă a GIST-urilor în ceea ce privește riscul de recurență și răspunsul la tratamentul cu inhibitori de c-Kit [11].

În ceea ce privește urmărirea pacienților, o monitorizare atentă trimestrială este necesară pe toată perioada tratamentului adjuvant datorită riscului de recurență/progresie. Totuși în caz de răspuns favorabil la ITK monitorizarea poate fi decalată de la 3 la 6 luni, mai ales după 5 ani de răspuns pozitiv, persistent, la tratament, deoarece există date care sugereaza scăderea riscului de recidivă în timp [11].

Concluzii

Lucrarea demonstrează eficacitatea şi siguranţa tratamentului cu imatinib în controlul progresiei bolii. Analiza mutaţională reprezintă o etapă obligatorie pentru evaluarea prognosticului şi răspunsului la tratamentul cu ITK.

Conflict De Interese

Autorii nu declară niciun conflict de interese.

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Case Report Open Access

Ginecomastia ca Semn de Prezentare Într-o Tumoră Testiculară Prezentare de Caz

Cristina Corina Pop Radu*

Disciplina de Endocrinologie; Universitatea de Medicină şi Farmacie, Târgu Mureş, Romania

***Corresponding author**: Cristina Corina Pop Radu, MD, Disciplina de Endocrinologie; Universitatea de Medicina si Farmacie, Târgu Mures, Str. Gh. Marinescu, No 38, 540139, Târgu Mureş, Romania, Tel: +40 (0) 265 21 44 10/236; Fax +40 (0) 744 64 71 72; E-mail: ccorinaradu@yahoo.com

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Abstract

Background: Orchitis tumor incidence is rare, about 2% of male malignancies. The pathology of tumoral orchitis has a maximum incidence between the ages 20-35, in children being more frequent the embryonal carcinoma and teratoma, in adult are met all types and in elderly predominates the seminoma. About 25% has endocrine secretory capacity. The incidence of gynaecomastia in adult men is reported as being 35-65%, depending on the criteria for diagnosing gynaecomastia and the age group. However, only 2% of men presenting with gynaecomastia are founded to have testicular tumours.

Case Report: We present the case of a 27 years old patient, diagnosed two years ago with testicular tumor. In diagnosis, the first sign was the unilateral gynaecomastia then neoplastic transformation of the left testicle was noted. The diagnosis was confirmed by ultrasound exam and tumoral markers (β human chorionic gonadotrophin over 5000 mUI/mL; alpha-fetoprotein at 12.3 UI/mL; lactate dehydrogenase at 1840 U/L). Left orchiectomy was performed. The pathological report showed a mixed tumor with germinal cells: embryonal carcinoma, teratoma and choriocarcinoma. The patient refuse adjuvant therapy and two months postoperatively pulmonary and vertebral metastasis were revealed. He followed radiotherapy, chemotherapy and neurosurgical treatment with complete remission.

Conclusion: We emphasize the importance of complete physical exam and testicular ultrasonography in any case of suspicion of testicular tumor. The multidisciplinary approach and treatment allows good results in advanced testicular tumors.

Keywords: Testicular Tumor; Paraneoplastic Gynecomastia

Introducere

Cancerul testicular are o incidență de 2% în oncologia generală masculină, ocupând locul patru între cancerele genito-urinare la bărbat și reprezentând cea mai frecventă neoplazie a adultului tânăr între 15-40 de ani (exceptând hemopatiile), fiind responsabil de o treime din decesele acestui grup de vârstă. Incidența este de 3-6 cazuri noi la 100.000 de bărbați/an, cu o tendință globală de creștere în ultimii ani în special la rasa albă (incidența maximă în SUA și Danemarca), în Asia și Africa incidența bolii fiind extrem de mică. La copii se întâlnește mai frecvent carcinomul embrionar (CE) și teratomul, la adult toate formele, iar la vârstnic predomină seminomul. Aproximativ 25% posedă capacitate secretorie endocrină. Tumorile celulelor germinale (TCG) reprezintă aproape 95% din tumorile primare testiculare. Se împart în tumori seminomatoase (45%) și non-seminomatoase (50%). Dintre cele nonseminomatoase (TCGNS) cele mixte sunt cele mai frecvente (40%). Teratoamele și terato-carcinoamele constituie 30% din leziunile non-seminomatoase. CE pur este relativ rar (20%). Choriocarcinomul (ChC) este cel mai rar (1%), dar și cel mai letal tip tumoral non-seminomatos [1]. Ginecomastia reprezintă un semn de activitate endocrină, incidența ei la bărbații adulți fiind de 35-65%, în funcție de criteriile de diagnostic și grupa de vârstă studiată. Totuși, doar 2% până la 11% a pacienților cu carcinom testicular se prezintă inițial cu ginecomastie [2,3].

Prezentare De Caz

Prezentăm un pacient în vârstă de 27 ani, care s-a adresat Serviciului de endocrinologie pentru apariția unei formațiuni tumorale la nivelul sânului drept de cca 7 luni. La examenul clinic s-a constatat retroareolar mamar drept, țesut glandular mamar de cca 3×2 cm, nedureros, mobil față de țesuturile supra- și subiacente, fără adenopatii axilare; testicul stâng mărit, cu suprafață neregulată, deformată, dur, nedureros (clasicul "testicul greu"). Fără alte modificări clinice obiective. Anamnestic relatează apariția ginecomastiei în urmă cu 3 luni și creșterea în volum dureroasă, însoțită de fenomene inflamatorii a testicului și hemiscrotului stâng cu o lună anterior prezentării la consultul endocrin. Ecografia mamară (Figure 1) a evidențiat în sânul drept un placard lenticular de țesut glandular mamar cu dimensiuni de 3,2×2 cm confirmând ginecomastia unilaterală dreaptă. Ecografia testiculară (Figure 2) a evidențiat un testicul stâng hipertrofiat (cca 8 cm), cu structură total dezorganizată, foarte inomogenă, cu aspect polichistic.

Explorările de laborator au evidențiat nivele mult crescute ale Alfa-Fetoproteina (AFP), gonadotrofinei corionice umane (beta HCG, BHCG), antigenului carcinoembrionar (ACE) și lactat-dehidrogenazei (LDH) (Table 1).

Computer tomografia a confirmat leziunea testiculară și a evidențiat perivezical și periseminal câțiva noduli adenopatici cu diametru de 4-5 mm, dar fără adenopatie retroperitoneală.

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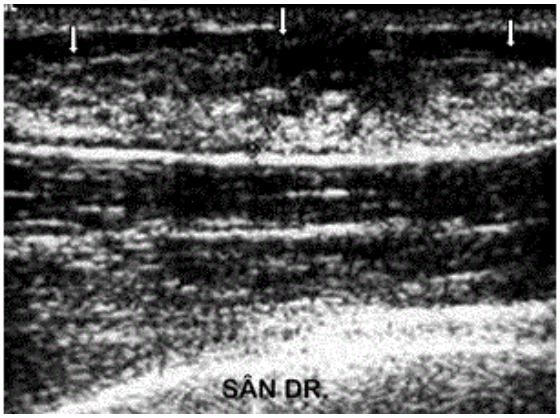

Figure 1: Ecografia mamară.

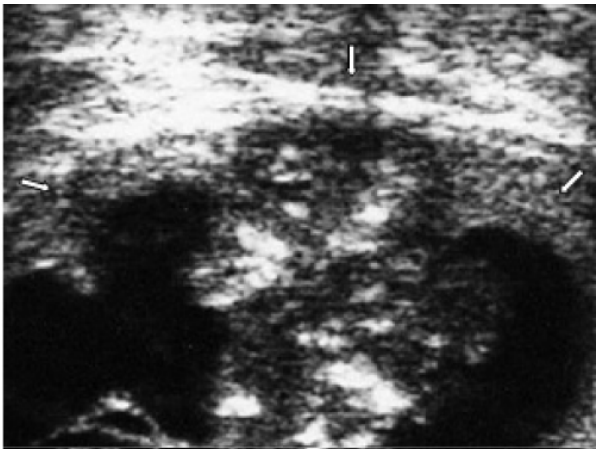

Figure 2: Ecografia testicului stâng.

Tumora a fost considerată în stadiul III și s-a realizat orhietcomia stângă urmând ca tratamentul să fie completat cu chimio- și radioterapie.

Examenul histopatologic a evidențiat macroscopic: piesă de orhiectomie de 80×50×45 mm cu funicul spermatic de 30×10 mm. Pe secțiune se remarcă o formațiune tumorală care înlocuiește aproape 90% din parenchimul testicular. Tumora are o culoare alb-cenușie cu multiple zone chistice. Examinarea microscopică a evidențiat o tumoră mixtă cu mai multe componente: choriocarcinom 20%, carcinom embrionar 40% și teratom 40% (Figure 3). Aspectul microscopic de teratom a fost confirmat de prezența de epitelii glandulare înconjurate de țesut conjunctiv și țesut neted (teratom matur), precum și zone de teratom imatur, cu epitelii de tip embrionar înconjurate de o stromă mixomatoasă.

Postoperator pacientul refuză tratamentul adjuvant, iar la două luni postoperator acuză scădere ponderală și dureri toraco-lombare care ulterior au devenit insuportabile și s-au complicat cu instalarea parezei membrului inferior stâng. Pacientul se internează în Institutul Național de Oncologie Budapesta unde se decelează nivele mult crescute de BHCG (>10.000 mUI/mL), se efectuează rezonanța magnetică nucleară (RMN) de coloană vertebrală și torace, care evidențiază diseminare pulmonară multiplă și metastazare la nivelul vertebrei toracice VIII (Figure 4).

Ulterior a fost supus unei cure chimioterapice: 4×BEP (Bleomicină, Etoposid, Cisplatin), cu administrarea la 4 luni de Carboplatin 700mg și Etoposid 180 mg. S-a efectuat iradiere cu 80 Gy pe segmentul afectat al coloanei vertebrale și după o ameliorare temporară a reapărut pareza la ambele membre inferioare care a impus efectuarea laminectomiei în scop de decompresie.

Discuții

Practic 95-97% din tumorile testiculare sunt maligne și germinale, astfel încât vechiul principiu clinic, conform căruia orice tumoră scrotală solidă trebuie considerată cancer testicular germinal până la proba contrarie, rămâne actual. De obicei se prezintă ca o masă unilaterală nedureroasă localizată în scrot. În aproximativ 20% din cazuri, primul simptom este durerea scrotală. În 10% din cazuri, cancerul testicular poate imita orhiepididimita, cu o întârziere consecutivă în stabilirea diagnosticului corect [4]. Demn de remarcat sub raport clinic este faptul că, descoperită în stadiu local franc tumoral, boala este în mod real în stadiu diseminat cu foarte rare excepții [4]. Netratată, boala duce inexorabil - fără remisiuni spontane sau accidente evolutive imprevizibile - la deces în primii doi ani de evoluție, moartea producându-se aproape întotdeauna datorită metastazelor pulmonare.

ChC are un indice de malignitate foarte crescut (practic incurabil), secretă BHCG, incidența maximă este între 15-35 ani, fiind foarte rar în forma pură. Se asociază cu ginecomastie bilaterală, asociată sau nu de creșterea AFP (markerul CE) și a hormonului lactogen placentar. Hiperproducția de BHCG induce creșterea de estrogeni, dar nu și de testosteron. Sunt tumori moi, mici, hemoragice, rapid metastazante. Microscopic este format din sincițiotrofoblaști și citotrofoblasti dispuși sub formă papilară [1]. Datorită agresivității sale deosebite, ChC înregistrează un curs rapid fatal prin hemoptizie masivă, deși adesea leziunea primară testiculară rămâne "ocultă" chiar la examenul piesei operatorii (leziune mică sau chiar "burned out tumor") [1,5].

CE reprezintă aproximativ 25% din tumorile testiculare, având incidența maximă la pacienții mai tineri. Macroscopic este o tumoră mai mică, cu suprafața neregulată prin consistența inegală, dezvoltată în plin parenchim testicular. Pe secțiune are aspect neomogen, alb cenușiu, cu zone întinse de necroză hemoragică. Pattern-ul microscopic include o mare varietate de celule epiteliale dispuse glandular papilar, cu caracter anaplastic, cu structură embrionară heterogenă. Este foarte agresiv [1,4].

Examenul de control la 6 luni de la chimioterapie arată absența ginecomastiei și paraparează în remisiune. Dozările hormonale nu au evidențiat disfuncții endocrine, cu excepția unui nivel ușor crescut de FSH explicabil în urma tratamentelor (FSH: 23,798 mUI/mL (2,1-18,6)); markerii tumorali erau de asemenea în limite normale. Imagistica evidențiază regresia leziunilor secundare și un aspect normal al testicului drept. Pacientul este considerat în remisiune și se continuă monitorizarea prin serviciul de oncologie.

Teratomul are o incidență mică în forma pură, fiind mai frecvent asociat CE (teratocarcinom). Macroscopic prezintă pe secțiune un aspect neomogen, pestriț, cu arii chistice, solide, cartilaginoase, osoase, sebacee, mucoase etc. Microscopic prezintă multiple structuri celulare specifice originii: glande mucoase (endoderm), țesut cartilaginos, mușchi (mezoderm), chisturi epiteliale scuamoase (ectoderm) cu

Table I: Markerii tumorali serici pre- şi post-operator; AFP alfa-feto-proteina; BHCG gonadotrofina corionică umană; ACE antigen carcino-embrionar; LDH lactat dehidrogenaza.

	Preoperator	1 lună postoperator	4 luni postoperator	Valori normale
AFP	12,3	1,0	0,770	< 7 UI/mL
BHCG	> 5000	1000	> 10.000	< 2,5 mUI/mL
ACE	20	6,7		< 3,4 ng/mL
LDH	1840	490		230-460 U/L

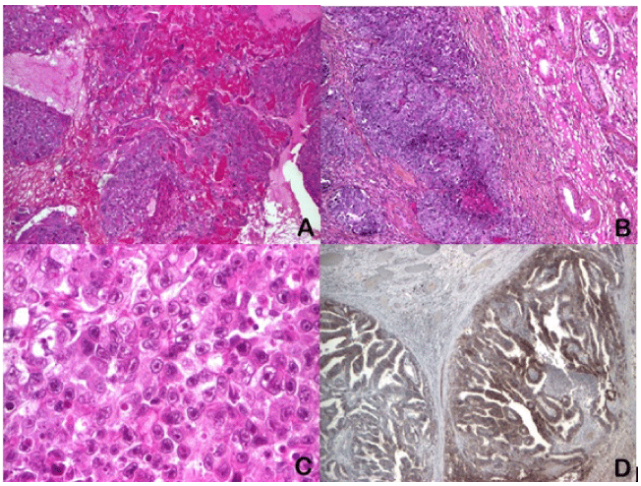

Figure 3: Examenul histopatologic: nu se observă celule tumorale în vasele capsule; tumora prezintă mai multe componente de: (A) Choriocarcinom - 20%, spaţii vasculare şi zone de necroză delimitate de sinciţio- şi cito-trofoblaşti; (B) şi (C) Carcinom embrionar - 40%, arhitectură papilară şi tubulară, celulele au limite imprecise, nuclei măriţi în volum, cu nucleoli vizibili, numeroase mitoze şi zone de necroze. IGCNU în tubii seminiferi restanţi (B). Imunohistochimic (D) zonele de carcinom embrionar exprimă CD 30 şi sunt negative la AFP.

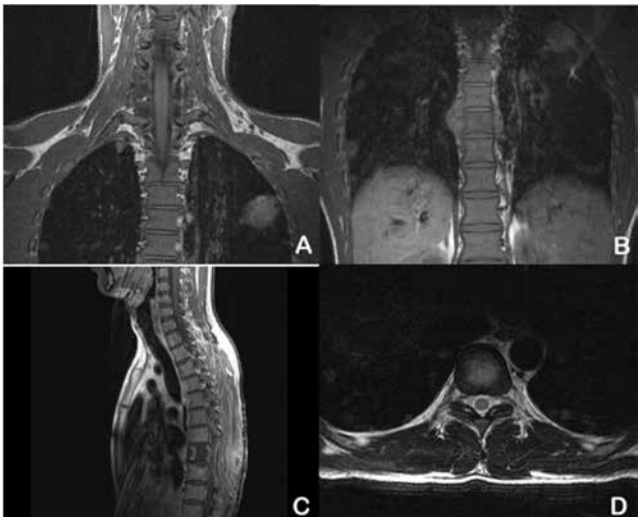

Figure 4: Imagistică prin rezonanţă magnetică toracică şi de coloană vertebrală: (A) şi (B) Diseminare pulmonară multiplă; (B) (C) şi (D) Corpul vertebrei T VIII cu modificări structurale patologice la nivelul întregului corp vertebral (aspect de metastază). Tumoră epidurală şi extra-osoasă cu o extindere semnificativă, cu compresia măduvei spinării. La nivelul T IX formaţiune patologică de dimensiuni mici cu densitate patologică (metastază).

diferite grade de diferenţiere: matur, imatur, cancerizat. Este mai putin agresiv, cu potenţial metastazant mai redus. Forma pură nu raspunde la chimioterapie [1,4].

Teratomul şi CE metastazează preponderent pe cale limfatică, iar ChC preponderent hematogen. Metastazele viscerale se produc în plămân (cel mai frecvent), ficat, oase, creier.

TCG pot metastaza cu altă structură histologică decât cea primară (în forma pură sau asociată), metastazele având capacitatea de a se transforma - spontan sau postcitostatic - într-o altă neoplazie (cel mai frecvent în sarcom) [1,4,6].

O treime din pacienţii cu TCG se prezintă la momentul diagnosticului iniţial în stadii diseminate de boală, cu metastaze limfoganglionare retroperitoneale sau viscerale [4].

Cauzele principale pentru întârzierea diagnosticului sunt: simptomatologia locală relativ nespecifică; lipsa de examinare a scrotului la examenul clinic de rutin (falsă pudoare); ignoranţa şi sentimentul de culpabilitate al pacientului care leagă leziunea scrotală de o falsă boală venerică.

Incidenţa ginecomastiei la bărbaţii adulţi este raportată la 35-65%, în funcţie de criteriile de diagnostic şi grupa de vârstă studiată. Totuşi, doar 2-11% a pacienţilor cu carcinom testicular se prezintă iniţial cu ginecomastie [2,3].

Ginecomastia reprezintă un semn de activitate endocrină, poate fi uni- sau bilaterală, poate preceda prezenţa tumorii testiculare palpabile sau tulburările hormonale şi apare în cazul ChC, CE, tumori cu celule Sertoli, tumori cu celule Leydig după vârsta de 30 de ani. Ginecomastia este de obicei atribuită dezechilibrului dintre estrogeni şi androgeni,

dar poate fi datorată în parte și acțiunii directe a LH-ului (hormon luteinizant) și HCG-ului la nivelul sânului [3,7-10].

Markerii tumorali serici, AFP, BHCG și LDH contribuie la diagnostic și stadializare, rolul lor major fiind în protocolul de urmărire, dinamica evoluției lor sub tratament reprezentând un indicator extrem de sensibil în aprecierea răspunsului terapeutic. Totuși nivele serice normale ale acestor markeri nu exclud diagnosticul de TCG. În general, o creștere a acestor markeri apare în 51% a cazurilor de TCG. Timpul mediu de înjumătățire plasmatică este de 5-7 zile pentru AFP și de 2-3 zile pentru HCG [4]. Nivelele de AFP și BHCG sunt crescute la 50-70%, respectiv 40-60% a pacienților cu TCG non-seminomatoase. LDH este un marker mai puțin specific, nivelul său fiind proporțional cu volumul tumoral. Cei mai fiabili și utilizați în practică sunt AFP, BHCG și gonadotrofina urinară totală. Specificitatea lor este maximă, iar sensibilitatea lor globală înregistrează 75% pentru AFP și 51% pentru BHCG. Cele mai mari nivele sunt atinse în ChC. Sensibilitatea metodei crește cu stadiul de boală. Radio-imuno-dozarea HCG în urina/24 de ore pare mai fidelă decât determinarea serică. Persistența nivelelor crescute ale markerilor serici după orhiectomie indică prezența bolii metastatice, dar normalizarea acestora nu exclude prezența metastazelor [4,6]. Markeri citogenetici și moleculari sunt disponibili doar în centre specifice cu scop de cercetare.

Factorii de risc pentru dezvoltarea cancerului testicular sunt istoricul de criptorhidie sau testicul necoborât (cel mai important factor de risc cunoscut), sindromul Klinefelter, istoricul familial de cancer testicular la rudele de gradul I (tată sau frați; studii cito-genetice ale materialului tumoral germinal au relevat prezența izocromozomului (12 p) al brațului scurt al cromozomului 12 în 80% din cazuri, justificând eticheta de marker diagnostic), prezența cancerului testicular în antecedente (risc de 500 de ori mai mare față de populația masculină normală), infertilitatea, expunere la DDT (pesticid organo-clorurat), atrofia testiculară (secundară orhitei urliene sau torsiunii de funicul spermatic - risc de 20 ori mai mare), hernie inghinală în copilărie, rasa albă, deficitul de 21-hidroxilaza, hipertonia de ACTH, administrarea de estrogeni mamei pe parcursul sarcinii. [4]

Diagnosticul diferențial se face cu tumefacții scrotale dureroase: orhiepididimita acută nespecifică, epididimita cronică nodulară, orhita granulomatoasă, torsiunea de funicul spermatic sau hidatida Morgagni (frecvente la copil); tumoră inghino-scrotală încarcerată sau strangulată; tumefacții scrotale nedureroase: hidrocel, hematocel, spermatocel, chist epididimar, varicocel, periorhită nodulară; tumori paratesticulare: tumori maligne sau benigne de epididim sau funicul spermatic. Forme clinice responsabile de erori de diagnostic sunt hidrocelul satelit tumorii în 10% din cazuri și "masca clinică" pseudoinflamatorie în 30% din cazuri [4].

Chimioterapia adjuvantă are meritul de a fi crescut curabilitatea globală a neoplaziei de la 35% (anii '70) la 95% în prezent. Este utilizată polichimioterapia, în cure de inducție, administrate la intervale de 3-4 săptămâni, în funcție de volumul tumorii metastatice (2-4 cure). Regimurile citostatice combină droguri foarte eficiente: cisplatin, bleomicina, actinomicina D, vinblastina, ciclofosfamida, methotrexat, etoposid și derivate mai puțin toxice și mai active: carboplatin, isofosfamida [11].

Monitorizarea răspunsului terapeutic presupune reevaluare stadială frecventă: determinarea markerilor (lunar), radiografie toracică (la 2 luni în primii 2 ani, la 4 luni în al 3-lea an și la fiecare 6 luni în anii 4 și 5), computer tomografie abdomino-pelvină, la nevoie toracică (la 3, 6, 9 și 12 luni) de la terminarea tratamentului, chiar și în caz de răspuns complet. Răspunsul incomplet obligă la reevaluarea factorilor diagnostici/prognostici inițiali și amplificarea schemei de tratament prin introducerea de modalități terapeutice mai agresive, "de salvare".

Protocoalele moderne de diagnostic, tratament și urmărire au făcut ca rata supraviețuirii *cancer-free* la 5 ani să atingă 100% pentru stadiul de boala locală și 70-95% pentru stadiile de boală diseminată incipientă și moderată [4,6,11].

Tratamentul și prognosticul cancerului testicular depinde într-o mare măsură de tipul histologic și stadiul clinic. În concordanță cu criteriile International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification [4,11], pacientul nostru a fost încadrat inițial în grupul cu prognostic intermediar (tumoră non-seminomatoasă, localizare primară în testicul-spațiu retroperitoneal, BHCG >5000, LDH > 500, fără metastaze cerebrale, hepatice sau osoase) cu o rată de supraviețuire la 5 ani de 80%. Totuși, prezența componentei de choriocarcinom (20%), subtipul histologic cel mai agresiv cu metastazare rapidă hematogenă determină un prognostic nefavorabil. Prezența carcinomului embrionar (40%) și a teratomului (40%) sunt de asemenea elemente de prognostic nefavorabil fiind asociate cu tendință de metastazare. Un alt factor important care contribuie semnificativ la vindecare este tratamentul complet și monitorizarea corectă, regulată a pacientului. În cazul pacientului prezentat întârzierea intervenției chirurgicale (din motive personale), ulterior refuzarea chimioterapiei postoperator cu o pauză de tratament de 4-5 luni au fost elemente care au contribuit la apariția complicațiilor (diseminare pulmonară și metastazare la nivelul coloanei vertebrale cu parapareză) și implicit la un prognostic nefavorabil (supraviețuire generală la 5 ani estimată la 48%).

Concluzii

Cazul prezentat se constituie într-un argument pentru importanța examenului clinic complet și corect, în particular, examinarea testiculară la bărbații cu ginecomastie. În caz de suspiciune este de preferat efectuarea ecografiei testiculare, chiar în absența modificărilor clinice și determinarea markerilor serici (AFP și BHCG).

Conflict De Interese

Autoarea nu declară nici un conflict de interese.

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Case Report Open Access

Prezervarea Splinei Într-Un Caz de Chist Splenic Voluminos

C Velicescu[1,2], **Mihaela Blaj**[1,3], **S Pădureanu**[1,2], **C Dogaru**[1,2], **I Dragostin**[2], **C Opincă**[2] **and C Burcoveanu**[1,2]

[1]*Departamentul de chirurgie, Universitatea de Medicină și Farmacie Gr. "T. Popa", Iași, Romania*

[2]*Clinica a IV a Chirurgie, Spitalul "Sf. Spiridon", Iași, Romania*

[3]*Clinica A.T.I. Spitalul "Sf. Spiridon", Iași, Romania*

[*]**Corresponding author**: Cristian Velicescu, MD, 4th Surgical Unit, "St. Spiridon" Hospital Iași, Bd. Independenței, No 1, 700111, Iași, Romania, Tel: +40 (0) 232 232 24 08 22; E-mail: cristianvelicescu@yahoo.com

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Abstract

Splenic cysts are uncommon, not frequently encountered in surgical practice. Generally, they are considered to be either parasitic or non-parasitic. We report the case of a young woman who presented with pain in the left upper abdomen quadrant and nausea. Ultrasonography and CT scan revealed a giant cystic lesion arising from the splenic hilum compressing the stomach and pancreas. At laparotomy a huge cyst was found which was affecting also the splenic vein and artery. Through a meticulous surgical technique it was possible to preserve the spleen in this particular case. Cystectomy with spleen preservation is the treatment of choice for spleen cystic lesions, especially in young patients, due to its immunologic functions.

Keywords: Splenic Cysts; Spleen Preservation Surgery

Introducere

Chisturile splenice neparazitare sunt boli rare, dar care, odată cu utilizarea pe scară largă a ecografiei abdominale, au început să fie mai frecvent diagnosticate. Cel mai frecvent sunt asimptomatice și diagnosticul este de regulă incidental în cursul unei examinări ecografice "de rutină". Totuși unii pacienți pot prezenta dureri abdominale nesistematizate în hipocondrul stâng [1].

Chisturile splenice sunt mult mai frecvente decât leziunile solide; chisturile "adevărate" trebuie să fie diferențiate de pseudochisturile de pancreas și de degenerare chistică în urma contuziei splenice sau a infarctului splenic.

Chisturile pot fi congenitale (chisturi epidermoide), infecțioase (abces sau chist hidatic) sau neoplazice (limfangiome sau angiom cu necroză tumorală). În funcței de etiologie, chisturile splenice reprezintă o indicație de splenectomie (totală sau parțială); cu toate acestea la pacienții tineri se preferă prezervarea splinei pentru a limita expunerea pacienților la infecții severe [2-5].

Prezentare Caz

Pacienta G.G. de 23 ani, din mediul rural, studentă, se internează pentru simptomatologie nespecifică: dureri în hipocondrul și flancul stâng mai ales în timpul efortului fizic, tulburări dispeptice. Pacienta nu prezintă antecedente heredo-colaterale sau patologice semnificative.

Examenul clinic decelează în hipocondrul stâng o formațiune tumorală dură, moderat dureroasă la palpare, care pare a aparține de splină. Probele biologice sunt în limite normale. Examenul ecografic evidențiază o formațiune chistică de 30×20 cm situată în hilul splinei fără limită de demarcație de parenchimul splenic, care amprentează corpul gastric și coada pancreasului și comprimă vena și artera splenică.

Examenul Computer Tomografic (CT) confirmă prezența unei formațiuni tumorale, rotunde, bine delimitate, de aspect chistic, de peste 20 cm diametru cu perete de 4 mm grosime și cu o calcificare de 4×5 cm; tumora este localizată la nivelul hilului splenic venind în contact cu marea curbură gastrică, corpul și coada pancreasului (Figure 1).

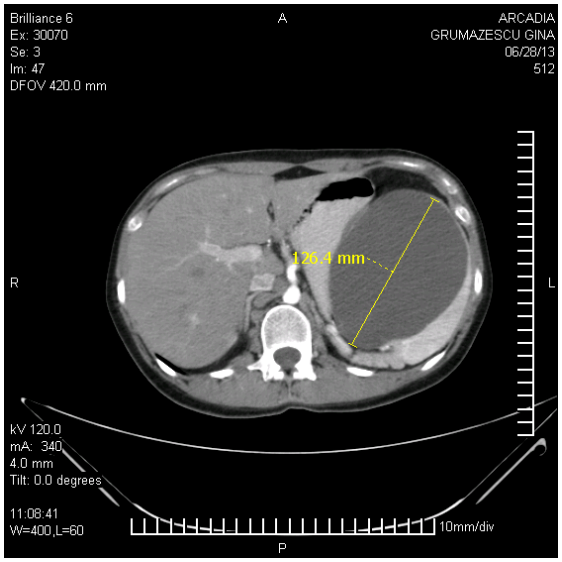

Figure 1: Examen CT cu substanță de contrast – formațiune chistică voluminoasă în hilul splinei.

S-a intervenit chirurgical sub anestezie generală; s-a practicat o incizie în "S" cu pătrunderea în cavitatea peritoneală. După secțiunea ligamentului gastro-colic se expune în un chist splenic gigant (cca 20 cm) situat în hilul splenic, cu o zonă de calcificare parietală de 4×5 cm, fără a se putea vizualiza inițial parenchimul splenic. Aspectul

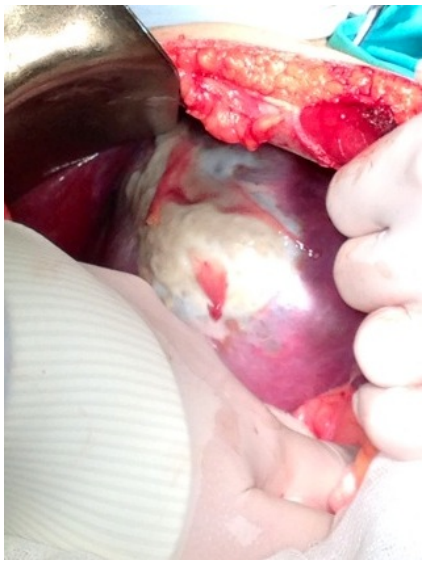

Figure 2: Aspect intraoperator - formațiune chistică splenică voluminoasă ce prezintă o calcificare parietală de 4×5 cm.

macroscopic este dificil de diferențiat de un chist hidatic splenic (Figure 2).

După izolarea câmpului operator și mobilizarea completă a chistului, se pune în evidență parenchimul splenic de aspect macroscopic, normal. Se practică ablația chistului (chistectomie ideală) cu minim de țesut splenic atașat chistului, hemostază atentă și prezervarea vaselor splenice (Figures 3 and 4).

Evoluția postoperatorie este favorabilă, cu reluarea tranzitului intestinal și a toleranței digestive; evaluarea ecografică de control la 72 ore postoperator, arată un parenchim splenic normal, cu flux prezent în vasele splenice.

Pacienta se externează la 5 zile postoperator și este dispensarizată periodic; la doi ani de la intervenție nu prezintă recidivă.

Examenul anatomo-patologic al peretelui chistului relevă prezența unui chist epidermoid, țesutul splenic adiacent având o structură normală.

Discuții

Chisturile splenice neparazitare sunt clasic împărțite în două categorii: *chisturile primare*, ce includ chisturile congenitale (epidermoide), hemangioamele chistice, limfangioame, chisturi dermoide, chisturi neoplazice, tapetate la interior de un strat celular epitelial/mezotelial, și chisturile secundare (pseudo-chisturi), ce se dezvoltă în parenchimul splenic posttraumatic sau postinfecțios, și care nu prezintă formal un strat celular bazal [1]. Există însă autori care împărtășesc altă opinie: toate chisturile neparazitare sunt de origine congenitală, iar traumatismul nu este un factor patogenic principal în apariția chistului [2].

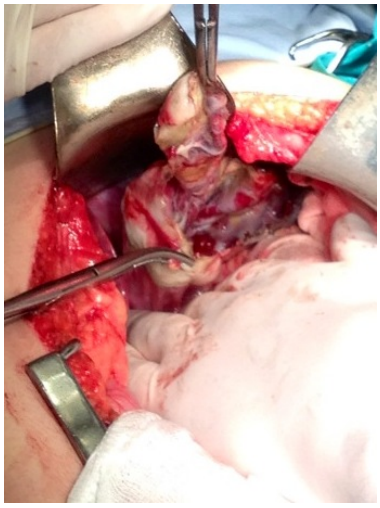

Figure 3: Chistectomia "ideală"; hemostază atentă la nivelul parenchimului splenic.

Chisturile splenice primare epidermoide sunt considerate de origine embrionară (disontogenetice), prezintă un vârf al frecvenței în copilărie și sunt o patologie mai des întâlnită în populația pediatrică [6], spre deosebire de chisturile secundare care totalizează peste 80% dintre leziunile chistice splenice neparazitare la adulți.

Dimensiunea medie a chisturilor splenice este de 13 cm, cu limite foarte variabile (4-20 cm) [7]. Cei mai mulți autori optează pentru intervenția chirurgicală dacă pacientul este simptomatic sau dacă dimensiunile chistului depășesc 4-5 cm, pentru restul leziunilor recomandându-se dispensarizarea clinică și imagistică [7]. Cu excepția leziunilor maligne, tratamentul chirurgical are drept obiectiv conservarea e parenchim splenic, mai ales la copii și tineri, pentru a evita complicațiile infecțioase [7,8].

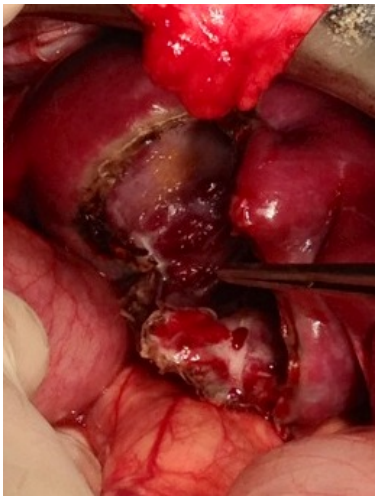

Figure 4: Aspect final după chistectomia "ideală"; de remarcat parenchimul splenic restant de aspect normal.

Chisturile splenice simptomatice au indicație operatorie clară. Chistectomia parțială laparoscopică sau clasică (fenestrare) este o metodă sigură și eficientă, cu morbiditate minimă însă cu rată de recidivă semnificativă [9]. Recidivele pot fi de mici dimensiuni și asimptomatice, astfel încât nu necesită întotdeauna reintervenții. Unele recidive simptomatice pot beneficia de drenajul percutan ecoghidat și doar un număr limitat de cazuri necesită reintervenție chirurgicală. Tratamentul optim este considerat a fi chistectomia ideală, realizată pe care clasică sau minim invazivă, ce permite evitarea recidivelor [10,11].

Concluzii

Chistectomia ideală reprezintă metoda optimă de tratament a chisturilor splenice primare (cu excepția neoplaziilor) având avantajul conservării parenchimului și funcțiilor splinei și permite evitarea morbidității generate de recidivele după chistectomiile parțiale.

Conflict De Interese

Autorii nu declară nici un conflict de interese.

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Case Report Open Access

Desmoid Tumor of the Thigh with Multiple Recurrences

Roxana Livadariu[1], **Daniel Timofte**[1*], **Mihaela Blaj**[2], **Delia Ciobanu**[3], **Lidia Ionescu**[1] **and Radu Dănilă**[1]

[1]*Department of General Surgery, "St. Spiridon" Hospital, "Gr.T. Popa" University of Medicine and Pharmacy, Iasi, Romania*

[2]*Department of Intensive Care, "St. Spiridon" Hospital, "Gr.T. Popa" University of Medicine and Pharmacy, Iasi, Romania*

[3]*Department of Pathology, "St. Spiridon" Hospital, "Gr.T. Popa" University of Medicine and Pharmacy, Iasi, Romania*

[*]**Corresponding author**: Daniel Timofte, MD, 3rd Surgical Unit, "St. Spiridon" Hospital Iași,Bd. Independenței, No 1, 700111, Iași, Romania, Phone: +40 (0) 232 24 08 22, E-mail: antimofte@yahoo.com

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Abstract

Background: Desmoid tumors are rare neoplasms of uncertain etiology arising from fascial or deep musculo-aponeurotic structures. Although with benign histological appearance and no metastatic potential, desmoid tumors are locally aggressive tumors with a high rate of local recurrence.

Case Report: The case of a 47 years old woman repeatedly operated for a recurrent desmoid tumor of the right thigh is presented. The initial radical excision was followed by adjuvant radiotherapy but local recurrence was diagnosed one year after. The pathology report revealed aspects of desmoid tumor. The patient was reoperated and subsequently referred for chemo- and hormonal therapy. A second recurrence occurred 20 months later and the patient was again operated with microscopic tumor free margins and positive long term outcome.

Conclusion: Desmoid tumors are benign tumors with unpredictable natural history. Best management involves a multidisciplinary approach. Concerning diagnosis, the best approach is performing a MRI examination. Wide surgical resection with adjuvant radiation therapy remains the main treatment option for local control.

Keywords: Desmoid Tumor; Surgery; Recurrence

Introduction

Desmoid tumors are rare neoplasms of uncertain etiology arising from fascial or deep musculo-aponeurotic structures that may occur at any age, but usually in young adults with peak prevalence between 25 and 35 years [1-3]. In adults, the tumor has a predilection in premenopausal women. Incriminated etiological factors are trauma or local surgery history, genetic factors like inherited mutation in APC gene (adenomatous polyposis coli) and high estrogenic states, including pregnancy [4]. Characterized by a benign histological appearance and no metastatic potential, desmoid tumors are locally aggressive tumors with a high rate of recurrence [5]. They may be localized in the abdominal wall, the bowel, and the mesentery (associated with familial adenomatous polyposis) or in extra-abdominal sites, such as the trunk and the extremities. The incidence of desmoid tumors ranges from 2 to 4 per million and almost half of them occur in the extremities and trunk [6].

Case Report

A 47 years old woman was hospitalized in our clinic for a swelling of the upper third of the right thigh, gradually increasing in size in the last 3 months. She had a history of an incomplete tumor excision on the same region, performed in another surgical unit 1 year ago. The pathological report showed at that time a fibroma with an important adipose structure. The local physical examination showed a tumoral mass located on the external face of the right thigh, under an old 10 centimeters long scar. The tumor was 8×4 cm, of firm consistency, painless, relatively fixed and seemed to infiltrate the subcutaneous tissue of the described area (Figure 1).

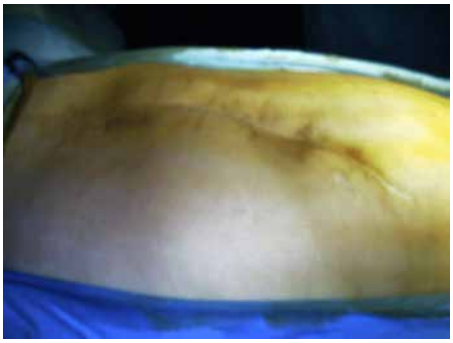

Figure 1: Preoperative aspect.

No motor, sensitivity or vascular alterations of the right lower limb were found. The CT scan revealed an expansive irregularly outlined tumoral mass on the upper third of the right thigh and gluteal region topography. The superior extremity of the tumor reached 1 centimeter above the upper bound of the right acetabulum and infiltrated the large and middle gluteal muscles. The tumor also invaded the semitendinosus, semimembranosus and right biceps femoris muscles without bone lesions. Under general anesthesia a wide tumor excision was performed with macroscopic tumor free margins (Figure 2).

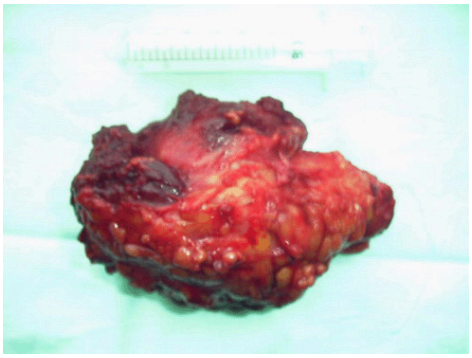

Figure 2: Operative specimen.

The postoperative evolution was uneventful and the patient was discharged after 8 days. The pathology report revealed a desmoid tumor. As recommended by the oncology board, adjuvant radiotherapy was performed. One year later the patient was readmitted for a 6×3 cm tumor mass, located on the posterior face of the lower third of the same thigh, clinically and radiologically suggestive for a local recurrence. Wide tumor excision was carried out and histological result was again desmoid tumor. The patient underwent for chemotherapy with metothrexate and vinblastine and antihormonal therapy with tamoxifen. After 20 months the patient was hospitalized for a new recurrence showing symptoms and signs of sciatic nerve paresis. The MRI showed an inhomogeneous 5.7×15.6 centimeters large tumor mass that invades almost entirely the right biceps femoris muscle extending to the vastus lateralis muscle. Superior to this one, the images showed another tumor mass located on the posterior face of vastus lateralis and major gluteal muscle, 5.3×10×3.5 centimeters large and with imprecise boundaries (Figure 3).

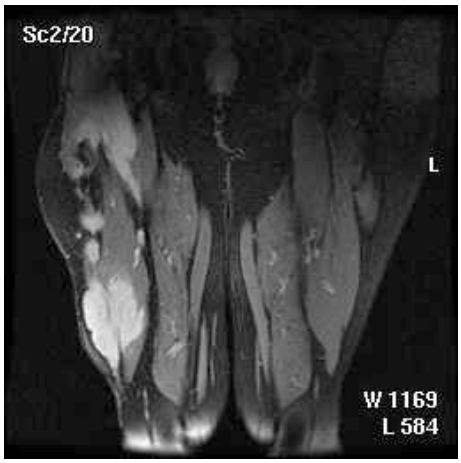

Figure 3: MRI aspect.

The patient was reoperated and a radical surgical excision with microscopically free margins (frozen section examination) was done. The postoperative follow-up showed no signs of recurrence after 6 months.

Discussion

Although computer tomography shows the extent of the tumor and its relationship to the neurovascular structures, magnetic resonance imaging is the modality of choice for the diagnosis and the evaluation of the tumor extent and the progression of the disease before and after treatment. It may also be helpful in differentiating tumour progression from post-surgical fibrosis [7]. Because multicentric and recurrent lesions tend to occur within the same limb or anatomic region, the MRI scanning of the entire extremity will be done once the diagnosis is made.

As far as the therapeutic options are concerned, surgery is the treatment of choice for extra-abdominal desmoid tumors. Wide excision with free tumor marginal resection is the goal standard of primary treatment. Re-excision for treating the recurrent disease is preferred by most authors, resulting in a cure rate similar to that of the primary surgical resection [8]. However, local control remains difficult. Radiation therapy with doses of 50–60 Gy is a viable alternative to surgery and a useful adjunct to incomplete resection of primary extra-abdominal desmoid tumors for the control of residual disease [8-11]. Radiation therapy alone can be used where surgery might lead to major morbidity and loss of function as well as for patients who have an inoperable tumor or gross residual disease after operative debulking [9]. The use of antihormonal therapy for the treatment of desmoid tumors is based on epidemiological observations for example, higher incidences of desmoids during and after pregnancy and reports of spontaneous tumor regression after menopause [12]. Studies have shown that virtually all desmoid tumors express nuclear estrogen receptor-β, but only a small subset of patients respond to antihormonal therapies [13]. Because COX-2 seems to play a role in the pathogenesis of desmoid tumors, treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAID) that inhibits COX may be effective [14]. A variety of other NSAID such as indomethacin and sulindac, a long-acting analog of indomethacin were associated with partial and complete responses in several nonrandomized retrospective studies, either alone or in combination with hormonal agents such as tamoxifen [15]. In contrast, in cases of an unresectable, rapidly growing and/or symptomatic and/or life-threatening desmoid tumor, traditional cytotoxic chemotherapy mainly with metothrexate and vinblastine may be the treatment of choice. Loco regional chemotherapy in the form of isolated limb perfusion for patients with locally advanced tumors is another alternative to systemic chemotherapy in patients with limb desmoids. Melphalan and recombinant human tumor necrosis factor-α are used as therapeutic agents with overall response rates of up to 80% [16]. The recurrence rates after wide local excision is reported as more than 40%, related to section margins, extra-abdominal localization of the tumor and age [8,17,18]. The predisposition of aggressive fibromatosis to locally recur is related to its infiltrative nature, the lack of pseudo capsule and possibility of diffusion along muscle fibres and fascial planes which makes it difficult for the surgeon to grossly identify the true extent of disease [19]. This may justify the high recurrence rate of the disease after adequate surgery and may also explain the distant recurrence on the same hip occurred to our patient.

Conclusions

Desmoid tumors are benign tumors with unpredictable natural history. Best management involves a multidisciplinary approach. Concerning diagnosis, the best approach is performing a MRI

examination. Wide surgical resection with adjuvant radiation therapy remains the main treatment option for local control.

Conflict of Interests

Authors have no conflict of interests to disclose.

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Surgical Techniques Open Access

Surgical Technique: Paratiroidectomia Minim Invazivă - Aspecte Tehnice, Experienţă Iniţială, Scurt Review al Literaturii

R M Neagoe[1], **S Bancu**[1], **Daniela Tatiana Sala**[2*] **and G Muhlfay**[3]

[1] *Clinica Chirurgie II, Spitalul Clinic Judeţean de Urgenţă Mureş*

[2] *Clinica Chirurgie II, Spitalul Clinic Judeţean de Urgenţă Mureş, Universitatea de Medicină şi Farmacie Târgu Mure*

[3] *Clinica ORL, Universitatea de Medicină şi Farmacie Târgu Mure*

***Corresponding author**: Daniela Tatiana Sala, Daniela Tatiana Sala MD, PhD, 2nd Surgical Unit, Emergency County Hospital Mureș, Str. Gh. Marinescu, No 50, 540136, Târgu Mureş, Mureş, Romania, Tel: +40 (0) 265 21 21 11; Fax: +40 (0) 265 21 57 68; E-mail: **salatatiana78@gmail.com**

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Abstract

Primary hyperparathyroidism (pHPT) is a common disease, in the majority of cases determined by a single solitary parathyroid adenoma; it is more frequently encountered among older women, between 50-60 years. Due to advances in imaging, preoperative localization of the hyperfunctioning or enlarged gland is almost always possible. In this perspective the classic bilateral neck exploration shifted to limited (focused) surgical approaches i.e. minimally invasive parathyroidectomy (MIP). The aim of this study is to do a short literature review of MIP surgical techniques and to present the surgical procedure we have used, along with our initial experience, respectively.

Keywords Parathyroid Glands; Primary Hyperparathyroidism; Parathyroidectomy; Minimally Invasive Parathyroidectomy; Mip

Introducere

Hiperparatiroidismul Primar (HPTP) nu este o boală rară, incidenţa acestuia fiind de 25/100.000 în populaţia generală [1] şi de 1/500 la femeile în postmenopauză [2]. De regulă boala este determinată de un adenom paratiroidian solitar (80-90% din cazuri); un număr redus de pacienţi prezintă hiperplazie multiglandulară (10-15%) iar în 1-4% din cazuri întâlnim adenoame duble sau carcinoame paratiroidiene [3]. Indicaţiile chirurgicale în HPTP sporadic se restrângeau iniţial la hipercalcemia severă (peste 12 mg/dL) cu hipercalciurie, boala osoasă asociată, vârsta peste 50 de ani, femei în postmenopauză [1-3]; la ora actuală aceste indicaţii sunt mai laxe, consensul fiind de a opera orice pacient cu HPTP şi reducerea densităţii osoase sau chiar asimptomatic, datorită riscurilor cardiovasculare sau a riscului malignitate hematopoetică, endocrină, a sânului, gastrointestinală sau renală [4,5].

Paratiroidectomia Minim Invazivă - Review al literaturii

Prima paratiroidectomie (P x) pentru HPTP a fost efectuată în 1925 de către chirurgul vienez Felix Mandl printr-o explorare bilaterală cervicală (bilateral neck exploration - BNE), procedeul fiind considerat şi la ora actuală un standard terapeutic [6]. În absenţa unor investigaţii imagistice specifice, explorarea bilaterală a tuturor glandelor paratiroide reprezenta singura metodă prin care intraoperator se putea distinge glanda adenomatoasă faţă de restul paratiroidelor, în general de aspect normal. Introducerea studiilor imagistice de localizare preoperatorie a adenoamelor paratiroidiene a deschis calea chirurgiei minim invazive paratiroidiene. Ultrasonografia cervicală de înaltă performanţă şi scintigrafia cu 99mTc-sestamibi au o sensibilitate de 85% respectiv 90% în decelarea adenoamelor paratiroidiene, sensibilitate ce ajunge la 95% prin combinarea celor două metode [7,8]. Avantajele demonstrate ale abordului minim invaziv sunt timpul operator mai redus [9,10], spitalizarea de scurtă durată şi costuri aferente mai reduse [11-13], avantaje cosmetice şi satisfacţia crescută a pacientului [11]. Mai mult, Bergenfelz şi colab. arată că la pacienţii operaţi minim invaziv incidenţa şi severitatea hipocalcemiei postoperatorii este mai mică faţă de grupul operat clasic [14]. Toate acestea coroborate cu faptul că paratiroidectomia minim invazivă (P x MI) are o rată de succes de 95%, similară cu intervenţia clasică de explorare cervicală bilaterală, explică tendinţă actuală de înlocuire a abordului clasic cu cel minim invaziv [15].

Sunt descrise diferite tehnici de PxMI şi din acest punct de vedere sunt posibile confuzii terminologice. O clasificare practică împarte PxMI în două categorii: P x MI prin incizii cervicale minime (Open Minimal Invasive Parathyroidectomy, OMIP) [16-20] şi P x MI endoscopice. Ultima categorie recunoaşte două tipuri de intervenţii: cele care nu folosesc insuflarea de gaz (gasless procedures) operaţia fiind video-asistată prin telescopul de mici dimensiuni introdus în plagă printr-o mică incizie (Minimal Invasive Video-Assisted Parathyroidectomy - MIVAP) [21,22] şi tehnicile total endoscopice, prin abord cervical, axilar sau la nivelul sânului [23-26]. Aceste tehnici endoscopice nu au cunoscut o largă răspândire la noi datorită constrângerilor de natură tehnică dar şi a unei incontestabile curbe de învăţare.

PxMI "clasice" presupun studii amănunţite imagistice preoperatorii de localizare a adenomului solitar paratiroidian, abordul chirurgical fiind ulterior "ţintit" la nivelul leziunii prin minime incizii cervicale; unii autori utilizează ca modalităţi de îmbunătăţire a ratei de succes terapeutic monitorizarea intraoperatorie a parathormonului seric (iPTH) sau radioghidajul intraoperator [16,27]. Paratiroidectomia minim invazivă radioghidată (P x MIR) se bazează principial pe capacitatea adenomului paratiroidian de a stoca pe o perioadă mai lungă şi într-o măsură mai mare radiotrasorul (99mTc-MIBI) faţă de ţesutul paratiroidian normal sau hiperplazic, tiroidă, ganglioni sau ţesutul grăsos cervical. Prima serie de PxMIR a fost descrisă de Martinez şi colab. în 1995 [25], însă metoda s-a răspândit în urma

studiilor publicate de Norman şi colab. [26,27]. Murphy şi Norman descriu "legea lui 20%", conform căreia orice structură cervicală a cărei radioactivitate măsurată intraoperator cu o gamma-probă depăşeşte 20% este cel mai probabil un adenom paratiroidian, aspecte confirmate şi prin studiile altor autori [28,29]. Limita cea mai importantă a acestei tehnici este legată de coexistenţa nodulilor tiroidieni, care pot fi sursa unor rezultate fals-pozitive; din acest motiv Casara şi colab. nu recomandă abordul minim invaziv atunci când HPTP se asociază cu o guşă nodulară [30]. O altă metodă de a îmbunătăţi rata de succes a unei PxMI este dozarea intraoperatorie a parathormonului seric (iPth). Metoda a fost popularizată de către Irvin şi Carneiro [31] şi se bazează pe timpul de înjumătăţire redus al iPth seric (2-3minute); extirparea chirurgicală a unui adenom paratiroidian, care este în 80-90% din cazuri solitar, este urmată la scurt timp (5 minute) de o reducere brutală de peste 50% a concentraţiei plasmatice a iPth seric, aceasta fiind dovada unei paratiroidectomii reuşite.

Cu toate că rolul acestor metode în îmbunătăţirea rezultatelor după P x MI este demonstrat [16,27] există autori ce raportează rate de succes similare utilizând tehnica minim invazivă "clasică", operaţia fiind efectuată uneori chiar în anestezie locală [13,15]. Aceştia descriu rezultate asemănătoare cu cele raportate în alte serii de PxMI, inclusiv endoscopice, dar notează faptul că succesul terapeutic este condiţionat de calitatea studiilor imagistice preoperatorii de localizare.

Tehnică Chirurgicală şi Experienţă Iniţială

Tehnica pe care o descriem şi pe care noi o utilizăm este cunoscută ca paratiroidectomie minim invazivă deschisă prin abord "ţintit" cervical lateral (focused lateral OMIP) şi presupune studii imagistice de localizare a adenomului paratiroidian, constând din efectuarea preoperatorie a scintigrafiei cu 99m-Tc sestamibi şi a ecografiei cervicale. În condiţiile în care scintigrafia (de preferat şi ecografia) evidenţiază adenomul solitar paratiroidian, pacientul poate fi selectat pentru abordul minim invaziv; în caz contrar sau atunci când sunt suspectate hiperplazia, adenoamele duble paratiroidiene, hiperparatiroidismul secundar sau leziuni tiroidiene asociate, se preferă explorarea cervicală bilaterală. Operaţia se efectuează în anestezie generală, anestezie pe mască laringiană şi locală sau doar anestezie locală. Abordul chirurgical se realizează printr-o incizie de 2-2,5cm plasată uşor lateral de inserţia medială a muşchiului sternocleidomastoidian (SCM); la debutul experienţei este de preferat marcarea regiunii sub ghidaj ecografic

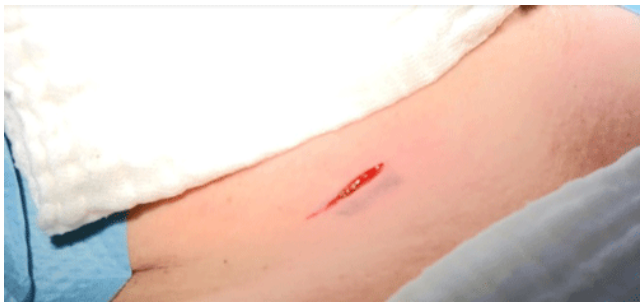

Figure 1: Incizia în abordul minim invaziv.

Spaţiul de lucru se crează prin disecţia şi îndepărtarea laterală a muşchiului sterno-cleido-mastoidian (SCM), respectiv medială a musculaturii subhioidiene şi lobului tiroidian omonim. Vasele mari cervicale (carotidă, vena jugulară internă) se îndepărteză lateral şi astfel se ajunge la nivelul fasciei prevertebrale

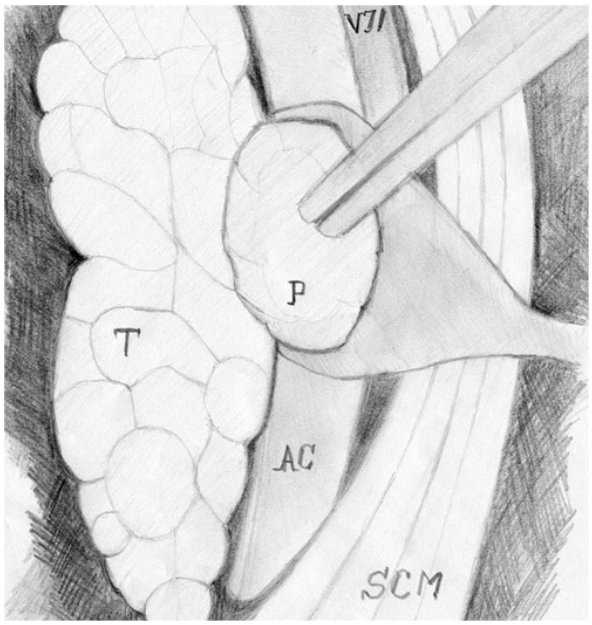

Figure 2: Repere chirurgicale în abordul minim invaziv.

AC artera carotidă; VJI vena jugulară internă; SCM muşchi sternocleidomastoidian; T tiroidă; P paratiroidă (adenom)

Tehnica presupune o disecţie exsanguă cu identicarea exactă a elementelor anatomice, inclusiv a nervului recurent. Adenomul odată identificat este disecat atent, de preferat fără efracţia capsulei sale, pentru a preveni paratiromatoza [32], ulterior superficializat şi rezecat prin cliparea vaselor

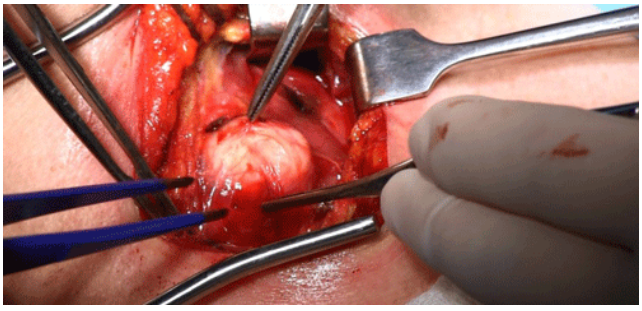

Figure 3: Excizia adenomului paratiroidian.

Este preferabil să se exploreze paratiroida ipsilaterală care, dacă este mărită în volum, ridică suspiciunea unei hiperplazii paratiroidiene; în aceste condiţii este recomandabilă conversia intervenţiei minim invazive într-o explorare cervicală bilaterală a tuturor glandelor paratiroide [33].

Fără a avea pretenţia unui studiu statistic, prezentăm în continuare experienţa noastră iniţială în abordul minim invaziv al adenoamelor paratiroidiene solitare. În perioada 2012-2014 în Clinica Chirurgie II

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Târgu Mureş s-au efectuat 11 paratiroidectomii minim invazive (P x MI) pentru diagnosticul 1HPT, toate operaţiile fiind efectuate de către aceeaşi echipă de chirurgi (RMN, DTS). Lotul nostru a inclus 8 femei şi 3 bărbaţi, cu vârste cuprinse între 27-68 de ani. Studiile de localizare s-au efectuat în toate cazurile; toţi pacienţii au beneficiat de scintigrafie 99mTc-MIBI care a evidenţiat sau a ridicat suspiciunea de adenom paratiroidian; această examinare, coroborată cu profilul biochimic tipic al bolii (hipercalcemie, hipofosfatemie), a reprezentat şi criteriul principal de includere a pacienţilor în lotul celor operaţi minim invaziv. Ecografia cervicală s-a efectuat la 10 pacienţi şi a confirmat leziunea descrisă scintigrafic în 8 cazuri (72,7%). Intraoperator leziunile descrise imagistic s-au confirmat la 10 dintre pacienţi, concordanţa diagnostică la lotul nostru fiind de 90,9%. Într-un singur caz, de altfel publicat de noi [34], am excizat minim invaziv un "adenom paratiroidian" stâng inferior de apoximativ 13 mm şi cântărind 2 g. Examinarea histopatologică a relevat o metastază de carcinom papilar tiroidian aflată în involuţie fibro-hialină, la o pacientă care de altfel fusese tiroidectomizată şi radioiodotratată cu 10 în urmă pentru acest diagnostic. La 8 pacienţi din lotul studiat s-a utilizat anestezia generală prin intubare orotraheală; în ultima perioadă am efectuat PxMI în anestezie generală pe mască laringiană potenţată cu o anestezie loco-regională de plex cervical superficial (3 cazuri), cu foarte bune rezultate

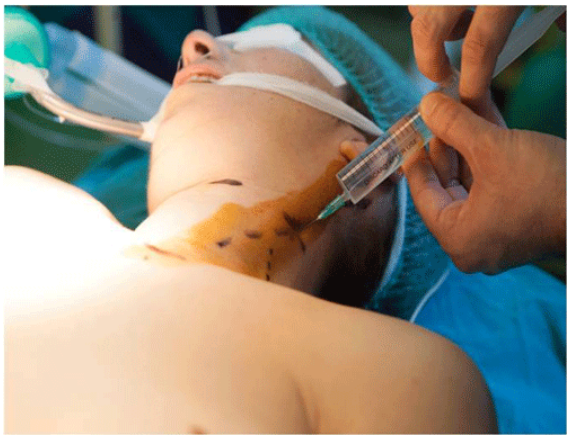

Figure 4: Anestezie de plex cervical superficial.

Operaţiile s-au efectuat după tehnica de paratiroidectomie minim invazivă deschisă prin abord "ţintit" cervical lateral (focused lateral OMIP) descrisă anterior; nu a fost necesară conversia la tehnica standard de explorare cervicală bilaterală în cazurile studiate. La primele 5 cazuri am utilizat marcarea regiunii cu ajutorul ecografiei preoperatorii; ulterior am intervenit doar pe baza datelor furnizate de studiile imagistice de localizare. În Tabelul I sunt redate aspecte ce privesc localizarea, dimensiunea şi datele biochimice la lotul nostru de pacienţi.

Nu avem posibilităţi tehnice de dozare intraoperatorie a parathormonului, însă valoarea acestuia, determinată la 48-72 de ore după operaţie s-a normalizat la 10 pacienţi; cazul ce a fost descoperit cu metastază de carcinom papilar a fost pierdut din urmărirea chirurgicală. O pacientă a prezentat o uşoară disfonie postoperatorie iar într-un caz am notat un minim hematom postoperator.

Concluzii

Paratiroidectomia minim invazivă prin abord lateral "ţintit" prin studii amănunţite preoperatorii de localizare a adenomului paratiroidian solitar este o soluţie chirurgicală în cazuri selecţionate de HPTP. Metoda presupune, pe lângă aportul obligatoriu al imagisticii, o experienţă în chirurgia endocrină cervicală, îndeosebi în cea paratiroidiană clasică; atunci când toate aceste condiţii sunt îndeplinite rezultatele postoperatorii sunt favorabile.

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Conflict de Interese

Autorii nu declară niciun conflict de interese.

Table I: Date anatomice şi de laborator.

Localizarea adenomului	
superior # inferior	4 superioare # 7 inferioare
dreapta # stânga	6 dreapta # 5 stânga
Mărimea adenomului (medie)	137 ± 82 mm
Calcemia preoperator (medie) (VN: 9-11mg/dL)	12,6 ± 0,7 mg/dL
Fosfatemia preoperator (medie) (VN: 2,7-4,5mg/dL)	1,82 ± 0,4 mg/dL
iPth (medie) (VN:15-68pg/mL)	
Preoperator	189,4 ± 96,4 pg/mL
Postoperator	25,3 ± 8,2 pg/mL

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Surgical Techniques Open Access

Surgical Technique: Lambouri Locale la Mână Utilizate în Reconstrucția Defectelor de Police–Tehnica Lamboului Littler

Mihaela Perțea[1*] **and Sorin Luncă**[2]

[1]*Clinica de Chirurgie Plastică și Reconstructivă, Spitalul Județean de Urgențe "Sf. Spiridon" Iași, Universitatea de Medicină și Farmacie "Gr.T. Popa" Iași, Romania*

[2]*Clinica II Chirurgie Oncologică Institutul Regional de Oncologie Iași, Universitatea de Medicină și Farmacie "Gr.T. Popa" Iași, Romania*

[*]**Corresponding author:** Mihaela Perțea MD, Department of Plastic and Reconstructive Surgery, "St. Spiridon Hospital", Iași, Independenței Street No 1, 700111, Iași, Romania, Tel: +40 (0) 232 24 08 22; E-mail: pertea_mihaela@yahoo.com

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Abstract

The thumb accounts for almost 50% of hand function, the pulp having a major role in ensuring it. Pulp injuries lead to marked disability, so preserve length, position, mobility, sensitivity thumb are just some of the goals that must be met for the techniques used in reconstruction of the thumb and its pulp. To rebuild the thumb pulp, Littler describes the technique that bears his name in 1953, using a neurovascular flap harvested from the cubital board of the third finger. Immediately after describing it, his technique proved to be successful as it brings the thumb pulp a sensitive tissue. As time has proved Littler flap attached advantages and some disadvantages. These have been linked mainly to the difficult and often incomplete cortical integration of the new pulp and donor site morbidity. The purpose of this article is to bring to attention the technique that should be considered whenever we face a thumb trauma with loss of the pulp region and exposure of the underlying structures.

Keywords: Thumb Trauma; Non-microsurgical Reconstruction; Litter Flap

Introducere

Deoarece policele asigură aproximativ 50% din funcția mâinii, având rol major în realizarea penselor police-digitale, a prizelor de forță, cilindrică dar și a mișcărilor fine, tehnicile utilizate pentru reconstrucția trebuie să aibă ca scop principal conservarea acestuia din punctul de vedere al lungimii, sensibilității, stabilității, mobilității, poziției, bineînțeles concordant fiind cu nivelul traumatismului. În timp, s-au găsit numeroase soluții în ceea ce privește modul de reconstrucție a defectelor pulpare ale policelui [1]. Au fost descrise numeroase tehnici atât nonmicrochirurgicale cât și microchirurgicale. Referindu-ne la tehnicile nonmicrochirurgicale pot fi menționate lambourile locale atât homo- cât și heterodigitale [2]. Lamboul neurovascular heterodigital Littler a fost descris de către cel căruia îi poartă numele în anul 1953, fiind utilizat pentru defectele volare de la nivelul porțiunii distale a policelui [3]. În 1983 Rose arată utilitatea lamboului Littler pentru acoperirea defectelor mari de la nivelul pulpei și feței volare a policelui [4]. Astfel, acest lambou are marele avantaj de a aduce o insulă cutanată de dimensiuni mari, sensibilă la nivelul feței volare a policelui, ajutând astfel, în multe cazuri la conservarea lungimii. Tehnica Littler reprezintă o soluție demnă de luat în seamă, mai ales în urgență, pentru pierderi importante de părți moi de la nivelul pulpei policelui cu expunerea structurilor subiacente. Acest lambou poate fi utilizat și asociat cu alte tehnici, ca soluție nonmicrochirurgicală de replantare distală a policelui [5]. Prezentăm tehnica lamboului neurovascular heterodigital Littler utilizat pentru acoperirea defectelor pulpare de la nivelul policelui.

Tehnica

Tehnica recoltării acestui lambou are mai multe etape: marcarea lamboului (după efectuarea testului Allen digital), recoltarea propriu-zisă a lamboului, aducerea lamboului pe zona receptoare și acoperirea zonei donatoare.

Desenul lamboului la nivelul zonei donatoare se face după măsurarea în prealabil a dimensiunilor defectului, precum și după efectuarea testului Allen digital, pentru a avea certitudinea existenței și a funcționalității celor două artere digitale colaterale ale degetului donator, cât și a degetului vecin zonei donatoare.

Intervenția chirurgicală se realizează sub anestezie loco-regională–bloc axilar și în câmp exsang utilizându-se un tournique la nivelul brațului.

Recoltarea lamboului se face de pe bordul ulnar al degetului III sau de pe bordul radial al degetului IV (borduri nefuncționale). În toate cazurile în care am utilizat acestă tehnică recoltarea lamboului s-a făcut de pe bordul radial al degetului inelar, considerând că morbiditatea zonei donatoare este mai mică la acest deget față de cea de la degetul trei.

Desenul lamboului se face la nivelul zonei donatoare respectând dimensiunile maxime posibile ale lamboului.

Disecția lamboului se începe de la nivelul laturii distale a lamboului asigurându-ne că pedicului vasculo-nervos este inclus în lambou, precum și mediul grăsos din jurul acestuia. Marginea distală a lamboului poate fi poziționată pînă în vecinătatea articulației interfalangiene proximale (AIFP). Se continuă disecția lamboului incizându-se marginile sale laterale (care reprezintă lungimea lamboului) și care nu pot fi poziționate decât până la nivelul liniei mediane a feței volare și respectiv aceleași linii la cea a feței dorsale a degetului, fără a le depăși. Disecția se continuă până la nivelul palmei. Marginea proximală a lamboului se poate poziționa până la baza primei falange. Lungimea lamboului precum și lățimea acestuia vor fi, de fiecare dată, date de dimensiunile defectului. De fiecare dată trebuie ales modul cel mai convenabil de recoltare a lamboului, astfel încât

morbiditatea la acest nivel să fie minimă și să existe un pat vascular bun pentru grefa de piele ce va acoperi ulterior zona donatoare

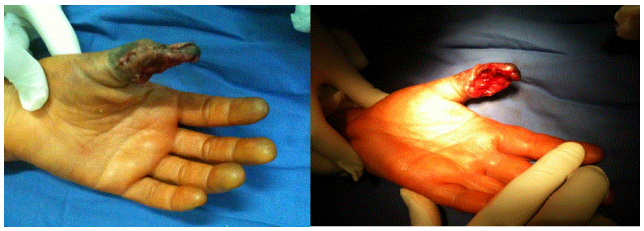

Figure 1: Traumatism de police cu defect pulpar.

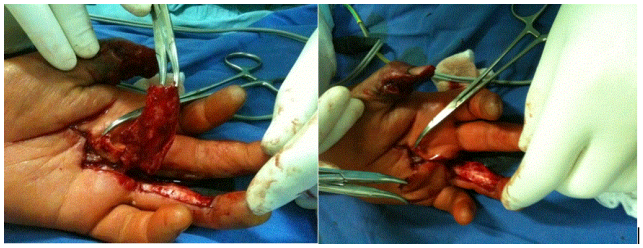

Figure 2: Ridicarea lamboului Littler de pe bordul radial al degetului IV și disecția sa până la nivel mediopalmar.

În palmă, disecția pediculului se face atent atât în ceea ce privește vasculoliza, urmată de ligatura și secționarea arterei colaterale a degetului vecin, cât și neuroliza intraneurală pentru separarea fasciculelor pentru lambou de cele care sunt pentru degetul vecin.

Odată lamboul ridicat, el trebuie transferat la nivelul situsului receptor. Această etapă operatorie se poate face prin două variante tehnice. Prima dintre ele constă prin tunelizarea lamboului la nivel tenarian. Acesta presupunere crearea tunelului, printr-o disecție atentă, la nivelul eminenței tenare. Tunelul trebuie să aibă dimensiuni care să permită deplasarea facilă a lamboului, poziționarea lui pe zona receptoare și să nu determine ulterior compresiuni la nivelul pediculului, care va rămâne la acest nivel, punând în pericol supraviețuirea lamboului. Cea de a doua variantă, în ceea ce privește transferul lamboului la nivelul zonei receptoare, este metoda deschisă și constă în incizarea tegumentului la nivel tenarian cu disecția marginilor acesteia, astfel poziționarea pedicului după aducerea lamboului la nivelul defectului să se facă la vedere, evitându-se astfel orice posibilitate de apariție a unei compresiuni la acest nivel.

Adus la nivelul zonei receptoare, lamboul se fixează cu puncte separate pe defect, poziționându-se astfel încât să se obțină o acoperire cât mai bună a acestuia (completă, corectă, estetică).

Zona donatoare se va acoperi cu grefă de piele toată grosimea recoltată dintr-un situs care să aibă cele mai bune rezultate estetice și eventual să nu fie utilizat un al doilea câmp operator. Poate fi utilizat eventual și un segment amputat (deget bancă). Lamboul poate fi utilizat și pentru defecte de până la 5 cm.

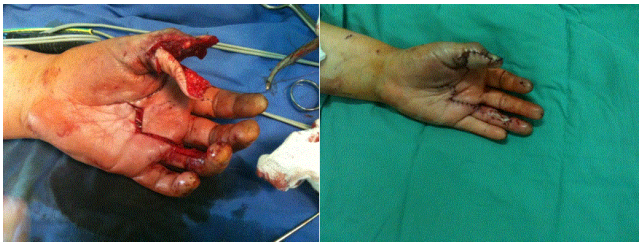

Figure 3: Tunelizarea lamboului și aplicarea sa pe zona receptoare.

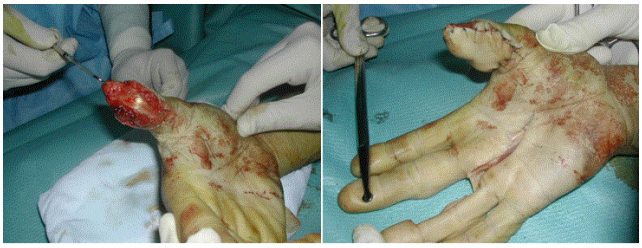

Figure 4: Defect pulpar police cu expunerea tendonului flexor lung de police și acoperirea cu lambou Littler.

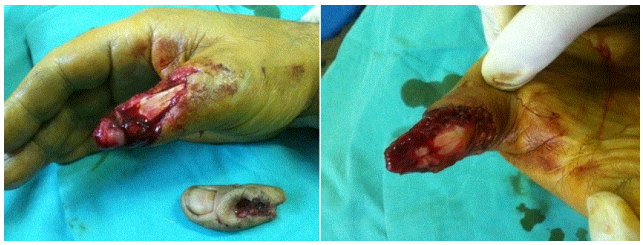

Figure 5: Traumatism de police cu defect pulpar de dimensiuni mari.

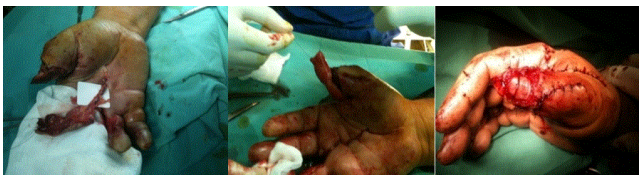

Figure 6: Utilizarea tehnicii Littler pentru reconstrucția de părți moi pulpare.

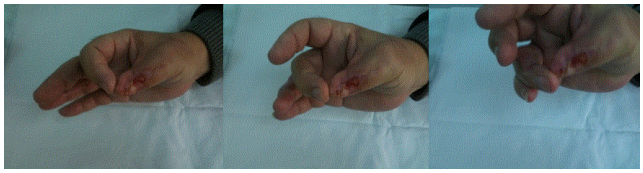

Figure 7: Rezultat la 60 de zile postoperator.

Pansamentul va fi făcut separat pentru fiecare dintre cele două zone implicate. Zona donatoare va fi acoperită de un pansament mai ferm pentru a facilita o aderare mai bună a grefei la patul receptor și pentru a ajuta la evitarea apariției eventualelor hematoame la acest nivel. În ceea ce privește pansamentul la nivelul lamboului, acesta trebuie să fie unul lejer pentru a nu determina eventuale compresiuni la nivelul acestuia sau a pediculului său. Uneori poate fi lăsată la vedere porțiunea centrală a lamboului pentru a putea urmări viabilitatea lui.

Complicațiile care pot apare pot fi atât la nivelul zonei donatoare cât și a celei receptoare. La nivelul situsului donor de lambou pot apare hematoame, în cazul în care hemostaza nu a fost făcută atent, care pot duce la o liză ulterioară a grefei de piele. De asemenea, rar, pot apare infecții sau necroze marginale atunci când manipularea tegumentelor în timpul ridicării lamboului au fost agresive. La nivelul lamboului, deci a zonei receptoare pot, de asemenea, apare hematoame sub lambou care pot periclita viabilitatea acestuia. Rareori, la distanță pot fi semnalate semne de infecție și uneori necroze sau doar suferințe la nivelul marginilor lamboului. Cea mai de temut complicație este necroza lamboului care poate surveni atunci când există compresiuni importante la nivelul pediculului sau ca urmare a unei disecții mai agresive care a produs eventuale leziuni vasculare.

Discutii

Scopurile care trebuie avute în vedere în cazul reconstrucției de police, după Heitmann și Levin, sunt: stabilitatea articulațiilor interfalangiene și metacarpofalangiene, asigurarea forței coloanei policelui, conservarea sensibilității la nivelul pulpei policelui, o poziție corectă a degetului 1 și o comisură cu o deschidere adecvată, asigurarea mobilității articulației carpometacarpiene cu musculatură intrinsecă [6]. Toate acestea pot fi realizate atunci când tehnica chirurgicală aleasă conservă lungimea policelui cât mai aproape de cea normală.

Urmărirea și atingerea scopurilor mai sus menționate într-o reconstrucție de police, sunt pentru a asigura o cât mai bună funcționare a penselor police-digitale, realizarea mișcărilor fine și prizelor de forță.

Traumatismele la nivelul policelui sunt variate ca și etiologie, mecanism de acțiune, nivel lezional. Toate acestea vor influența alegerea tehnicii chirurgicale care va fi utilizată în reconstrucția policelui. De aceea, alegerea tehnicii chirurgicale va fi în funcție de: vârsta pacientului, starea generală, nevoile funcționale, nivelul leziunii, mecanismul de acțiune, leziunile asociate (leziuni la nivelul degetelor lungi, eminenței tenare, altor segmente ale membrului toracic), mâna dominantă, etc. Se va cere acordul pacientului, ținându-se cont și de cerințele acestuia având în vedere morbiditatea care va rezulta la nivelul zonei donatoare.

Dintre tehnicile nonmicrochirurgicale de reconstrucție a policelui distal, ne-am oprit asupra lamboului Littler, deoarece are o serie de avantaje.

Acest tip de lambou este unul de gradul III în clasificarea care ține cont de tehnică și dificultatea acesteia, ceea ce însemnă că se face cu disecția fără dificultate a unui pedicul vascular mare, dar este necesară disecția prealabilă pe cadavru, iar lamboul trebuie făcut de un operator deja antrenat [2].

În ceea ce privește indicațiile, acest lambou trebuie utilizat atunci când există traumatisme cu pierderi tisulare la nivelul pulpei policelui la persoane vârstnice, la care un eventual lambou liber transferat nu poate fi luat în discuție, în cazul în care pulpa policelui a fost inițial reconstruită cu un lambou insensibil sau după o replantare, când reconstrucția nervoasă nu a putut fi efectuată [2]. Se mai folosește când tarele asociate ale pacientului nu permit utilizarea lambourilor de la distanță, când pacientul nu este de acord cu o zonă donatoare de la distanță.

Dintre avantajele acestei tehnici menționăm faptul că acest lambou aduce la nivelul pulpei policelui o insulă cutanată sensibilă cu textură și calități asemănătoare celei pierdute, sechelele funcționale și estetice fiind minime [2]. Arcul de rotație al lamboului este mare putându-se orienta astfel încât zona receptoare să fie acoperită adecvat, putându-i-se da forma dorită. Nu este necesară o imobilizare în ușoară flexie a policelui, ca în cazul lamboului O'Brien. Zona donatoare se află în același câmp operator fără a fi necesară utilizarea microscopului operator.

Dezavantajele tehnicii, constatate în timp, au fost legate de posibilitatea reintegrării corticale a neopulpei, care de cele mai multe ori este lentă, sensibilitatea tactilă a acesteia rămânând la nivelul zonei donatoare. S-au mai adus în discuție și incovienentele legate de morbiditatea zonei donatoare. De-a lungul timpului s-a încercat diminuarea acestor dezavantaje.

S-a încercat secționarea nervului conținut în lambou și reanastomozarea sa la capătul proximal al nervului colateral digital ulnar al policelui [7]. Rezultatele estetice și funcționale nu au diferit mult în acest caz față de cele obținute folosind tehnica Littler clasică [7]. Fenomenul „dublei sensibilități", a fost rezolvat de reanastomozarea nervoasă [7]. În ceea ce privește discriminarea 2PD, rezultatele au fost mai bune în cazul folosirii tehnicii Littler clasice [7].

S-a mai încercat modificarea tehnicii prin același timp de reanastomoză, reanastomozarea nervoasă fiind făcută la oricare nerv colateral digital al policelui traumatizat [8]. S-a constatat că în ceea ce privește prezența paresteziilor, acestea au fost menționate mai frecvent la cei la care s-a utilizat tehnica Littler clasică. Testele Semmes-Weinstein și 2PD static și dinamic nu au avut diferențe importante în cazul reanastomozării nervoase față de tehnica clasică. Reintegrarea corticală a neopulpei a fost mult mai bună în cazul folosirii tehnicii modificate [8].

Cu toate avantajele și dezavantajele sale lamboul Littler rămâne una dintre tehnicile de bază care pot fi utilizate pentru acoperirea defectelor pulpare de la nivelul policelui, cu indicațiile mai sus menționate [9-11].

Concluzii

Tehnica Littler sau tehnica lamboului neurovascular heterodigital are avantajul posibilității de a de a acoperi defectele mari de la nivelul

pulpei policelui cu o suprafață cutanată cu textură asemănătoare celei pierdute, sensibilă, fără a utiliza un alt câmp operator, cu risc minim de a se necroza, comparativ cu alte lambouri locale. Este un lambou fiabil și sensibil cu sechele funcționale și estetice minime. Poate fi asociat altor tehnici pentru o reconstrucție cât mai bună a policelui. În ceea ce privește morbiditatea zonei donatoare precum și reintegrarea corticală dificilă a neopulpei pot fi diminuate și respectiv îmbunătățite, atunci când acurateții tehnicii chirurgului i se alătură o bună cooperare a pacientului și o muncă susținută a kinetoterapeutului.

Conflict De Interese

Autorii nu declară niciun conflict de interese.

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Multimedia Article Open Access

Ventral Hernia Repair by Laparoscopic Approach, how to do it

R Moldovanu*

Department of Surgery and Oncology, Les Bonnettes Hospital, Arras, France

Department of Surgery, University of Medicine and Pharmacy "Gr. T. Popa" Iaşi, Romania

***Corresponding author**: Radu Moldovanu MD, PhD, Les Bonnettes Hospital, Arras, France, Department of Surgery and Oncology, 2 rue Dr. Forgeois, BP 20990, 62012, Arras, France, Tel: +33 (0) 3 21 15 43 88, Fax: +33 (0) 3 21 60 22 58, E-mail: rmoldovanu@gmail.com

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Abstract

Background: Laparoscopic approach for ventral hernias is associated with decreased hospital stay, reduced risk of infection and low recurrence rate compared with the open repair techniques. However, these good outcomes depend of several surgical techniques related key points.

Aim: The aim of this paper is to present and highlight these "critical" key points.

Method: The paper presents the procedure in a step-by-step manner; operative room set-up, peritoneal access and trocars placement, abdominal wall defect exploration, accurate mesh placement with a minimum 4 to 5 cm mesh overlap of the hernia defect and an adequate mesh fixation. The different key points as mesh insertion and unrolling as well as mesh placement and fixation are highlighted. Several data from literature were also discussed.

Conclusion: The laparoscopic ventral hernia repair is a feasible and safe procedure. The respect of procedure's "critical" key points allows the best outcomes in term of hospital stay, postoperative pain and morbidity.

Keywords: Ventral Hernia; Laparoscopy; Mesh Repair

Background

Laparoscopic Ventral Hernia Repair (LVHR) is associated with decreased hospital stay, low rate of postoperative infection and low rate of recurrence compared with open repair techniques [1,2]. To achieve these better outcomes several key points were described: adequate patients' selection, choice of the peritoneal cavity entry and capnopneumo-peritoneum creation, trocars placement, adhesiolysis, abdominal wall exploration with careful inspection of parietal defect(s) (site(s), dimensions), mesh insertion, deployment and fixation [3-6]. Furthermore, these key points were the subject of several guidelines [7-9].

The aim of this video is to highlight these key points that allow "reliable outcomes" [5].

Patients' Selection

LVHR has to be the first choice for all the patients with primary or incisional hernias, even for the small parietal defects (smaller than 2 cm) [7]. The technique is especially preferred for medium size parietal defects (less of 10 cm in diameter) in obese patients because it reduces the wound infection rate as well as overall morbidity [7,10,11]. However there are several relative contraindications as large parietal defects (over 10 cm in diameter) and severe comorbidities (contraindication for laparoscopy and general anesthesia) [7]. Even the LVHR appear to be a "straightforward technique" an adequate training is mandatory [9]; in this way it is important to carefully select the first 10 to 20 cases in term of parietal wall defect diameter, BMI (body mass index), comorbidities and "estimated" adhesiolysis.

Surgical Technique Data

Operating room set-up

The procedure is performed under general anesthesia. The patient is in supine position. It is preferred to put both arms in adduction along the body to allow the cure of eventual occult inguinal hernia diagnosed during laparoscopy.

Trocars and instruments

Usual laparoscopic instruments are used: fenestrated graspers, hook, monopolar scissors, bipolar grasper, disposable taker (absorbable tacks). Usually 4 trocars are used: 1×10 mm; 2×5 mm; 1×15 mm. The use of 15 mm trocar is mandatory to allow the mesh abdominal insertion in order to avoid the mesh to skin contact (risk factor for postoperative wound infection [7]). The standard classical instruments include Kelly and Kocher graspers, Farabeuf retractors, Metzenbaum scissors, Hegar needle holder. A Reverdin needle is also necessary for the placement of expandable meshes or transfascial sutures.

Capto pneumoperitoneum creation and gaining access to peritoneal cavity

The peritoneal access has to be tailored with patient's and hernia's characteristics. In this way, for the median hernias with a parietal defect smaller than 2 cm a direct access through the hernia sac is generally used, placing a 15 mm trocar. For larger median parietal defects, an open access several centimeters afar from hernia site is preferred. For the lateral hernia a midline open access is used. A "direct view" 15 mm trocar can be also used as alternative to open

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access. The use of Veress needle should be avoided because the high risk of small bowel injuries which may preclude mesh placement, because these patients usually have previous surgery and adhesions [5-7,12].

After the capto pneumoperitoneum creation in function of hernia site, the patient is placed in a 15 to 30° Trendelenburg (or anti Trendelenburg) and a lateral right or left side tilt.

Trocars placement

After patient lateral tilt placement, the other three trocars are adequately inserted, under laparoscopic view control, in the right (or left) flank as far as possible from hernia site. The 10 mm trocar is placed to the mid distance between costal margin and Anterior Superior Iliac Spine (ASIS); the other two 5 mm trocars are placed 2 cm under the costal margin and respectively 2 to 5 cm from ASIS, in order to allow triangulation, adhesiolysis, mesh placement and fixation. Additional 5 mm trocars can be placed to complete adhesiolysis or to perform the concomitant inguinal hernia repair.

Adhesiolysis

The adhesions have to be carefully divided by sharp dissection and monopolar coagulation to avoid intestinal injuries. In the same time the herniated viscera are re inserted in the abdomen and carefully checked for ischemia or coagulation injuries.

Abdominal wall exploration

After the complete adhesiolysis a complete exploration of the abdominal wall including inguinal arias is performed. I prefer to divide the liver round ligament and the hernia sac to clearly view the aponeurosis to diagnose the occult white line hernias ("swiss cheese parietal defect") [5].

Parietal defect(s) assessment

For the concomitant groin hernia a Transabdominal Pre-Peritoneal (TAPP) procedure is performed during the same operation.

The ventral abdominal wall defects are carefully assessed and measured to choose the adequate mesh size. The external defect measurement on insufflated abdomen is usually performed even it overestimates the defect size [5]. It is very important to choose a mesh size which overlaps with a minimum 5 cm in all directions the parietal defect(s), to avoid postoperative mesh shrinkage and recurrence [1-9].

Mesh preparation and insertion

Two-side faces meshes are used to avoid visceral adhesions. An expanded polytetrafluoroethylene [ePTFE] mesh coated with polydioxanon is generally used [9]. However, from several months a new generation of meshes, which are expandable, is used in our surgical department: lightweight monofilament polypropylene mesh coated with a hydrogel barrier based on Sepra® technology. For the non-expandable meshes, 4 cardinal sutures are placed 1 cm from the edges and the sites of transfascial sutures are marked.

The mesh is rolled and inserted into the abdomen through the 15 mm trocar, avoiding the skin contact.

Mesh deployment and fixation

After the mesh is brought into the peritoneal cavity, it is unrolled and placed in the proper position, to overlap 5 cm in all directions the parietal defect using cardinal sutures (no expendable mesh) or inflated balloon (expendable mesh).

For no expendables meshes the cardinal sutures are passed through the abdominal wall using a Reverdin needle; then, the sutures are pulled up and tied (transfascial suture). A circumferential fixation by absorbable tacks placed every 5 cm along the mesh edge and 1 cm from the mesh edge is then performed; another line of tacks is placed circumferentially 2 to 3 cm from the first tacks line.

For the expendables meshes, the fixation is performed only by tacks placed circumferentially in double crown as described above. The balloon is then removed by a 5 mm trocar.

For the suprapubic hernia, the peritoneum is opened and a wide dissection is performed in Retzius space to expose the pubic bone, bilateral Cooper's ligaments, and the femoral vessels, like in TAPP procedure. The mesh is then fixed to pubic bone and Cooper using tacks. Peritoneum is also closed using tacks.

Exsufflation and closure

After complete mesh fixation, a careful inspection of the mesh and abdominal wall is performed to verify the hemostasis; the pneumoperitoneum is progressively exsufflated. It is important to remove the pneumoperitoneum under laparoscopic view control to check the hemostasis and mesh deployment.

The parietal defects smaller than 2 cm are generally closed by a monofilament non absorbable running suture. Trocars sites are infiltrated with long lasting local anesthetics.

Postoperative Care

The patients receive analgesics and anti-inflammatory therapy (Paracetamol 1 g×4/day; Nefopam 20 g×4(6)/day; Ketoprofene 100 mg×2/day) as well as thrombotic prophylaxis (low weight heparin). The patients are generally discharged at day 2.

Discussion

The LVHR is not a gold standard procedure even its advantages, in term of length of hospital stay; postoperative morbidity and recurrence rate were demonstrated.

The operative time seems to be longer for LVHR especially during the learning curve and when mesh fixation is performed by transfascial sutures; in this way, new technologies like expandable meshes decreases operation time [13].

The postoperative morbidity rate is variable and depends of parietal defect size, BMI and comorbidities [7-9]. The postoperative acute pain is more intense when transfascial sutures are performed [7-9]; in the same time the postoperative pain depends of number of tacks and is apparently less important when absorbable tacks have been used [7-9].

The average recurrence rate for LVHR is less of 4% and depends of defect type (primary or incisional) and size, mesh defect overlap and type of mesh fixation (apparently transfascial sutures have an advantage in term of recurrence) [7-12]. However a recent meta-

analysis about mesh fixation devices failed to demonstrate the advantages of transfascial sutures [14].

LVHR was found cheaper than open techniques in term of total costs especially due to lower readmission rate and rapid return to daily activities/work [7-9].

Probably the most important disadvantage of LVHR is the higher direct costs then open techniques [8]; this is especially important for developing countries. In this way, different alternative non validated techniques (e.g. intraperitoneal poly-propylene mesh on a greater omentum "bed") are considered cheaper but total costs (wound infection, visceral injuries due to mesh direct contact, intestinal obstruction, recurrences, readmissions, longer hospital stay etc.) are far to be correct estimated.

Conclusions

LVHR is a well-accepted option in the treatment of hernias. The respect of procedure's "critical" key points allows the best outcomes in term of hospital stay, postoperative morbidity and recurrence.

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