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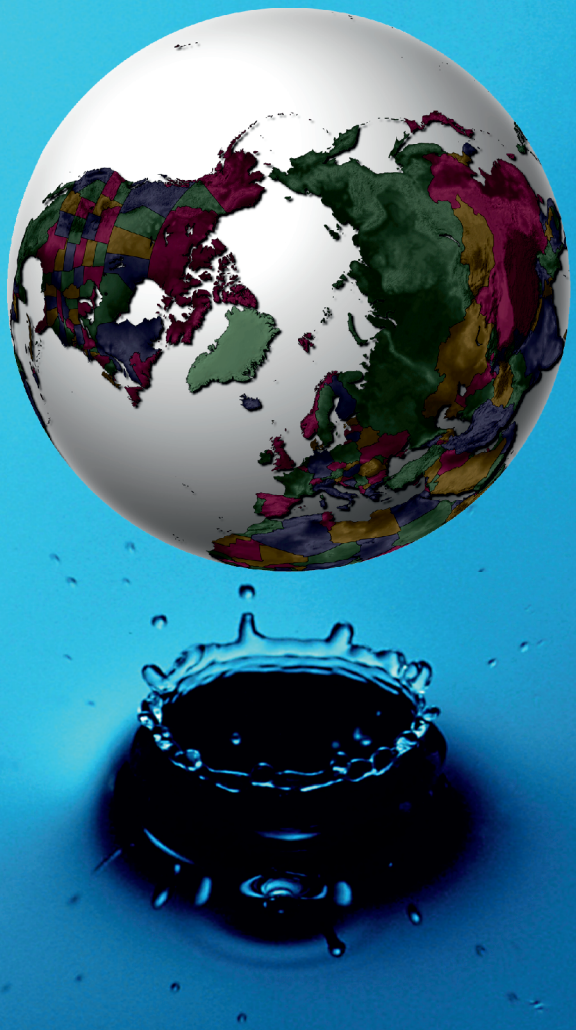

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Review Article Open Access

Current Concepts in the Presentation, Diagnosis and Management of Primary Hyperparathyroidism

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Abstract

Background: Primary hyperparathyroidism (PHPT) is a common clinical endocrine disorder. It is the most common cause of hypercalcemia in the outpatient setting. This review presents a brief summary of the new trends of presentation, diagnosis and management PHPT.

Data Sources: PubMed (National Library of Medicine) articles, and Memorial Library archives of the University of Wisconsin System.

Conclusions: PHPT occurs at any age, but it is most commonly seen in people over the age of 50 years and postmenopausal women. The current presentation of PHPT shifts from the classical symptomatic form to the asymptomatic form; however, parathyroidectomy is still the treatment of choice for both symptomatic and asymptomatic forms. In the past, bilateral neck exploration and intraoperative identification of all 4 parathyroid glands was the standard of treatment, nevertheless, nowadays, with the introduction of the preoperative and intraoperative localization techniques, the minimally invasive parathyroidectomy has evolved.

Keywords: Primary Hyperparathyroidism; Presentation; Diagnosis; Management

Introduction

Primary hyperparathyroidism (PHPT) is defined by an abnormal increase in the intrinsic activity of the parathyroid gland(s) that result in elevated parathyroid hormone (PTH) levels [1,2]. It is one of the most common endocrine disorders and is the most common cause of hypercalcemia. PHPT is one of the most common endocrine disorders and is the most common cause of hypercalcemia, which increases morbidity and mortality that result from cardiovascular, renal, and musculoskeletal pathologies. PHPT affects 1 in 500 females and 1 in 2,000 males aged >40 years, with a peak incidence in post-menopausal women. In the US, Europe, and Australia, the reported estimated incidence rates range from 25 to 30 per 100,000 person years, and the prevalence range from 1 to 21 per 1,000 individuals [1-4].

PHPT has been a recognizable disease since the 1920s in both Europe and the US [5]. The first parathyroidectomy was performed in 1925 by Felix Mandl in Vienna, Austria; since then, the diagnosis and management of PHPT have progressed [5]. The purpose of this article is to review the current trends of PPT presentation, work-up, and management.

Anatomy and Physiology

Humans typically have four parathyroid glands located at the posterior capsule of the thyroid gland; in up to 15% of individuals have more than four and up to 3% have three identifiable glands [6]. The superior parathyroid glands arise from the IV pharyngeal pouch and migrate to the cephalad thyroid gland; they are usually located at the cricothyroid junction, 1 cm from the recurrent laryngeal nerve and the inferior thyroid artery. Inferior parathyroid glands arise from the III pharyngeal pouch and migrate caudally with the thymus; they are usually located on the posterolateral aspect of the inferior pole of the thyroid gland. Normal parathyroid glands are yellow or brown in color, oval in shape, 3–7 mm in length, and 30–40 mg in weight [7,8].

A parathyroid gland consists of chief cells, oxyphilic cells, a thin fibrous capsule, and a network of adipose tissue, blood vessels, and glandular parenchyma [8]. Chief cells secrete PTH, which consists of 84 amino acid polypeptides. The normal serum PTH level range is 15–72 pg/mL, with a half-life of 2–4 min. Seventy percent of PTH metabolism occurs in the liver and 30% in the kidneys [9-11]. PTH is regulated by serum calcium, phosphorus, and vitamin D metabolites. The total normal calcium level should be 8.8–10.2 mg/dL (ionized calcium 2.2–2.6 mmol/L) to ensure optimum physiological functions [9-11]. PTH levels are inversely proportional to serum calcium levels, as high serum calcium levels decrease PTH release [5-7] and low serum calcium levels increase PTH secretion. This relationship enhances renal tubular calcium reabsorption, urinary phosphate excretion, osteoclast-mediated bone resorption, and the conversion of 25-hydroxyvitamin D3 into 1,25-hydroxyvitamin D3, which increases calcium absorption from the bowel [9-11].

Etiology

Ninety-five percent of PHPT cases are sporadic. Of these cases, 75–85% result from a single adenoma, 2–12% result from double adenomas, 10–15% result from multiple gland hyperplasia, and <1% result from parathyroid carcinoma [12-14]. Patients with multigland disease tend to have PTH levels of <100 pg/mL, a negative preoperative localization, or several neurocognitive symptoms [15,16]. Serum calcium levels of >14 mg/dL (3.5 mmol/L) or a palpable neck mass with elevated PTH may indicate parathyroid carcinoma [17]. Familial endocrine disorders occur in approximately 5% of PHPT cases and

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frequently present in younger populations with a positive family history of neuroendocrine tumors or hypercalcemia (Table 1). Patients with inherited hyperparathyroidism and multigland disease have a higher risk of persistent and recurrent disease [14].

Head and neck radiation increase the risk of developing PHPT by two- to three-fold [18]. Additionally, the use of thiazides may lead to mild hypercalcemia by reducing urinary calcium excretion, and the use of lithium may lead to increased serum calcium and PTH by decreasing the sensitivity of the calcium-sensing receptor to calcium [19,20]. Although the pathogenesis of PHPT is not well known, studies have shown that gene mutations, growth factors, calcium-sensing receptor antibodies, and chronic vitamin D deficiency are possible underlying pathologies [20].

Presentation and Clinical Forms

Patients may present with symptoms of hypercalcemia or PTH excess or they may be asymptomatic; however, the severity of hypercalcemia is not directly linked to the severity of symptoms [21]. Symptomatic PHPT has been linked to the classic aphorism of "stones, bones, groans, and psychiatric overtones." However, asymptomatic PHPT is linked to high serum calcium levels in routine biochemical evaluation, in which patients present in early stages before the development of classic symptoms of PHPT [12]. The most common presentations of PHPT are hypercalciuria, which are seen in almost 40% of PHPT patients, and kidney stones, which have an incidence of 15–20%. Other renal presentations of PHPT include nephrocalcinosis, polyuria, and reduced creatinine clearance (CrCl) [22,23]. Additionally, patients may have low bone mineral density (BMD) in their cortical bones. Almost 15% of patients have vertebral osteopenia and 2% have osteitis fibrosa cystica. PHPT may be associated with rheumatic conditions, such as gout and pseudogout [24,25].

Patients may develop gastrointestinal symptoms, such as nausea, constipation, peptic ulcers, and pancreatitis [26], or neuropsychiatric symptoms, such as depression, dementia, confusion, lethargy, social function impairment, psychosis, and coma [27]. Patients with PHPT have a higher prevalence of hypertension, cardiac and coronary artery calcification, left ventricular hypertrophy, conduction abnormalities, glucose intolerance, endothelial dysfunction, and abnormalities in the coagulation and fibrinolysis pathways [28,29]. In pregnant women, PHPT increases the risk of preeclampsia and fetal defects, such as intrauterine growth retardation, low birth weight, preterm delivery, intrauterine fetal death, neonatal tetany, and permanent hypoparathyroidism [30]. Because of the routine use of screening tests and BMD measurements, 80% of PHPT cases are asymptomatic or present with nonspecific symptoms, such as fatigue, mild depression, bone pain, weakness, memory loss, decreased concentration, and sleep problems [12].

Several clinical forms of PHPT exist, according to severity. Classic PHPT is characterized by the elevation of both calcium and PTH, and patients usually have typical symptoms [1,12]. Mild PHPT is characterized by elevated PTH or calcium in isolation, mild elevations in both, or asymptomatic disease, and is associated with smaller adenomas and a higher incidence of multigland disease. Normocalcaemic PHPT is characterized by elevated PTH and normal serum calcium [12,31,32].

Differential Diagnosis and Work-up

Hypercalcemia has several causes (Table 2), but malignancy is the second most common cause [19]. The diagnosis of PHPT is usually made biochemically, based on serum calcium, PTH, and phosphate levels. Elevated levels of serum calcium and PTH are associated with a 95% risk of a diagnosis for classic PHPT; however, patients may have normal levels of phosphate, calcium or PTH. Serum calcium levels should be repeated and all cofactors should be controlled. Normal ionized serum calcium, elevated PTH levels, and no signs of secondary hyperparathyroidism are consistent with normocalcemic PHPT [31-36]. Undetectable PTH levels rule out PHPT, but raise the possibility of cancer-associated hypercalcemia, while elevated PTH levels in a patient with a malignant condition suggest concomitant PHPT (Figures 1 and 2). Administration of oral calcium will suppress PTH in patients with secondary hyperparathyroidism [32-36].

In addition, serum 25-hydroxyvitamin D, CrCl, chloride, protein electrophoretic pattern, alkaline phosphatase, creatinine, uric acid and urea nitrogen, urinary calcium, blood hematocrit, serum magnesium, and erythrocyte sedimentation rate are valuable for diagnosis [36]. Elevated serum chloride is found in approximately 50% of patients with PHPT because PTH decreases the resorption of bicarbonate in the proximal renal tubule, thus increasing the resorption of chloride [36]. Plain-film radiography of the skeleton is not recommended; however, BMD should be evaluated by a dual-energy X-ray absorptiometry scan of the lumbar spine, hip, and distal radius [37]. Moreover, renal ultrasonography or computed tomography (CT) scanning is recommended if the history suggests nephrolithiasis [32-35]. Genetic testing should be considered only in patients with recurrent disease, multiple gland involvement, a young age, a family history of PHPT or multiple endocrine neoplasia (MEN), or other features of MEN, to rule out genetic disorders [32-35]. Furthermore, according to the National Institutes of Health (NIH) guidelines, a 24-h urine collection to measure calcium and creatinine is no longer required for all patients, although it should be obtained if a concern for familial hypercalcemic hypocalciuria (FHH) exists, as these patients do not benefit from parathyroidectomy [33-35]. Patients with FHH are typically asymptomatic and have mild hypercalcemia and a positive family history of hypercalcemia [38]. A 24-h urine calcium of less than 100 mg/L or a calcium-to-CrCl ratio of 0.01 is consistent with FHH [39]. Calcium Sensing Receptor (CASR) DNA sequencing test can be considered to confirm or rule out a suspected diagnosis of FHH [40].

Localization Techniques

Preoperative localization techniques should not be used to confirm the diagnosis of PHPT, but should be considered to guide the endocrine surgeon intraoperatively, to evaluate for ectopic glands, and to assist in the planning of minimally invasive parathyroidectomy (MIP) [40]. Nuclear (sestamibi) imaging using 99m technetium (99mTc) is considered to be the standard technique for preoperative imaging of parathyroid glands. In a dual-phase technique with 99mTc sestamibi imaging, both the thyroid tissue and abnormal parathyroid tissue incorporate 99mTc sestamibi quickly after intravenous administration. Hyperactive parathyroid tissue has a slower washout rate compared with thyroid tissue. Recently, 99mTc tetrofosmin was introduced, with similar imaging protocols as 99mTc sestamibi, but with a slightly different mechanism of accumulation in tissues. The 99mTc sestamibi protocol has a sensitivity of 70–90%, and is may be affected by underlying biochemistry, vitamin D deficiency, pedunculated adenomas, mobile adenomas, superiorly located adenomas, thyroid nodules, the small adenomas, and thyroid suppression before imaging [41-43].

Several retrospective studies found that sestamibi scans are a useful preoperative localization tool for PHPT, especially in cases caused by a single adenoma. These studies reported that surgeon interpretation and radiology experience increased the likelihood of localization [44,45-47]. The authors recommend that sestamibi scans be reviewed by experienced parathyroid surgeons, rather than relying on radiological interpretation alone [45-47]. Anderson et al. reported 62% sensitivity and 83% specificity of radiological interpretations [45]. Chen et al. reported that the sensitivity of the surgeon (93%) was higher than both high-volume (83%) and low-volume (72%) radiologists [46]. Neychev

Table I: Genetic Mutations of Familial Hyperparathyroidism Disorders

Disorder	Type of inheritance	Gene	Chromosomal Location	Protein
MEN1	AD	MEN1	11q13	Menin
MEN1- variant	AD	CDKN1B/p27	12p 12-13	
MEN2A	AD	RET	10q2110q11.2	Receptor tyrosine Kinas
HPT-JT	AD	HRPT2	1q21-q321q25	Parafibromin
FIHPT	AD	HRPT2 MEN1	1q21-q3211q132p13.3-14	Parafibromin
ADMH	AD	CASR	3q13-21	Calcium-sensing receptor
FHH	AD	CASR	3q13-21	Calcium-sensing receptor
NSHPT	AR/AD	CASR	3q13-21	Calcium-sensing receptor

Abbreviations: MEN1, multiple endocrine neoplasia type 1 gene; MEN2A, multiple endocrine neoplasia type 2 gene; HPT-JT, hyperparathyroidism-jaw tumor syndrome; FIHPT, familial isolated hyperparathyroidism; ADMH, autosomal dominant moderate hyperparathyroidism; FHH, familial hypocalciuric hypercalcemia; NSHPT, neonatal severe hyperparathyroidism; AD, autosomal dominant; AR, autosomal recessive; CDKN1B/p27, cyclin-dependent kinase inhibitor 1B (p27Kip1); RET, RET proto-oncogene; HRPT2, hyperparathyroidism 2 gene; CASR, calcium-sensing receptor gene.

Table II: Causes of Hypercalcemia

Category	Disorder	Comments
Parathyroid Dependent	Primary hyperparathyroidism	Sporadic, or familial
	Tertiary hyperparathyroidism	Chronic renal failure or vitamin D deficiency
PTH Independent	Vitamin intoxication	Vitamin A or D intoxication
	Granulomatous disease	Sarcoidosis, berylliosis, tuberculosis
	Malignancy	Humoral hypercalcemia of malignancy mediated by PTHrP, especially lung, head, and neck squamous cancers, and renal cell tumors
		Local osteolysis, mediated by cytokines like multiple myeloma, and breast cancer
		Hodgkin's lymphoma
	Medications	Thiazide diuretics, or lithium
		Calcium antacids (Milk-alkali syndrome)
	Other hormone-related	Hyperthyroidism, adrenal insufficiency, acromegaly, or pheochromocytoma
	Genetic disorders	Familial hypocalciuric hypercalcemia
	Other	Immobilization, with high bone turnover, Paget's disease, bedridden child
		Recovery phase of rhabdomyolysis
		Parenteral nutrition

Abbreviations: PTHrp, parathormone related peptide

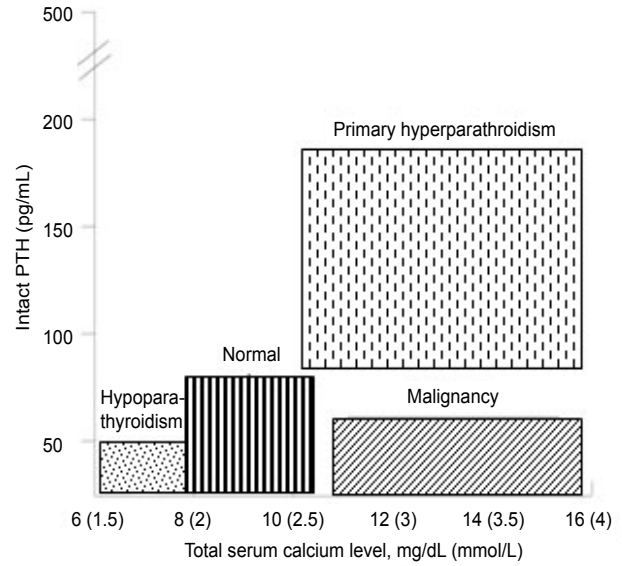

Figure 1: Extracted Blue Node

et al. reported a sensitivity of 58.6% for nuclear medicine physicians, compared with 81.9% for both a surgeon and a nuclear medicine physician [47].

Parathyroid ultrasonography is an accessible, inexpensive, and noninvasive test. Using a linear ultrasound transducer with a frequency of 7.5–10 MHz, it localizes enlarged parathyroid glands and evaluates the thyroid gland to rule out any synchronous thyroid disease. Normal parathyroid glands cannot be visualized by ultrasonography, but parathyroid adenomas appear as hypoechoic or anechoic, discrete, and oval homogenous hypervascular solid masses. Larger adenomas may show cystic changes, lobulations, occasional calcifications, and increased echogenicity because of fat deposition. However, the sensitivity of ultrasonography fluctuates between 22% and 80%, because it is user dependent and limited in its ability to localize retroesophageal, retrotracheal, retrosternal, intrathyroidal, mediastinal, small, and deep cervical glands [41,48,49]. Vitetta et al. found that sonography performed by an expert was associated with an appreciably superior diagnostic yield than 99mTc sestamibi [50]. Thus, ultrasound can be used as the main method for preoperative localization of pathological parathyroid tissues [50].

Classic CT is limited in imaging parathyroid adenomas, but four-dimensional parathyroid CT (4DCT), in which four phases are used to identify parathyroid lesions, can provide anatomical and functional information on the parathyroid gland. CT scans identify parathyroid adenomas in 90% of the cases. While false-positive findings can be seen for thyroid nodule, tortuous vessel, or laterally displaced esophagus, false-negative results can be seen in cases of small or ectopic adenomas or distorted neck anatomy due to previous surgery. However, ionizing radiation is a limitation of 4DCT for routine localization of parathyroid disease; thus, it should be used selectively in patients whose parathyroid glands are not localized on routine imaging. Single-photon emission CT (SPECT) can help to differentiate the parathyroid gland from thyroid tissue, with a sensitivity of 87% for solitary adenomas, 30% for double adenomas, and 44% for multigland disease. Research shows that a combination of SPECT and CT with various dual-phase imaging can boost the accuracy of localization [43,51,52].

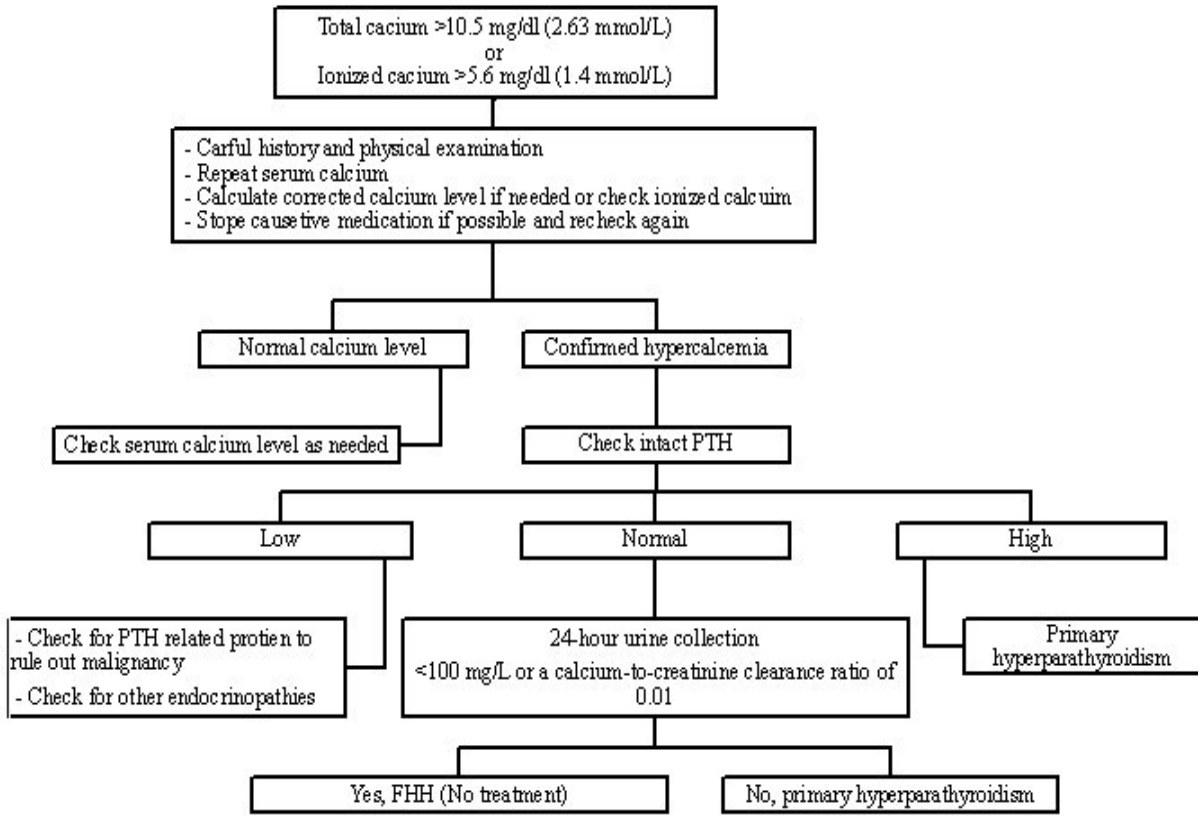

Figure 2: Evaluation of Hypercalcemia

Magnetic resonance imaging (MRI) is a good choice for imaging if there is a possible concern for radiation exposure or nephrotoxicity. Typical MRIs involve axial images of the neck and mediastinum. While normal parathyroids are usually not detected on MRI images, parathyroid adenomas are seen as soft-tissue masses, with low-to-medium signal intensity on T1-weighted images and high signal intensity on T2-weighted images. After gadolinium contrast administration, abnormal parathyroid glands show a strong enhancement on T1-weighted images that are similar to conventional T2-weighted imaging [42].

Parathyroid arteriography and parathyroid venous sampling are invasive tests that should be offered only when the results of noninvasive methods are negative. On angiograms, parathyroid adenomas appear as hypervascular oval lesions with smooth margins. Selective PTH venous sampling can be drawn to localize the hyperactive parathyroid gland. A gradient of at least two-fold in PTH levels confirms the location of hyperactive parathyroid tissue. Intraoperatively, a similar selective technique can be performed to localize the hypersecreting parathyroid gland and/or confirm curative surgical resection [53-55].

The IoPTH assay is used to determine the appropriateness of a parathyroid tissue resection [56,57]. Numerous criteria have been suggested to confirm the sufficiency of parathyroid resections [58]; however, the most widely accepted is the Miami criterion. With a 97% accuracy rate, IoPTH is measured based on a 50% drop from an initial PTH level reading to the level measured 10 min after gland excision. When PTH levels remain elevated after an excision of the suspected gland, a bilateral neck exploration may be necessary to locate the remaining hypersecreting tissue [56,57]. The IoPTH test is also reliable in mild cases, even if PTH is not elevated [59].

Management

Patients with serum calcium levels of 1214 mg/dL (33.5 mmol/L) may not require immediate treatment if this elevation is chronically well tolerated. However, an acute rise in calcium levels may lead to dehydration or cardiovascular or neurologic complications, which require more aggressive measures. In addition, patients with serum calcium levels of >14 mg/dL (3.5 mmol/L) require treatment, regardless of symptoms. Thus, patients with severe hyperparathyroidism-induced hypercalcemia should be hospitalized, and urinary catheterization and central venous pressure monitoring should be considered. Initial treatment should include intravenous saline solution to gradually replace lost fluids and increase urinary calcium excretion [2,33,34,40,60,61]. Once fluid repletion is accomplished, loop diuretics may be used to decrease renal calcium reabsorption and promote urinary excretion. Calcitonin 200 IU once every 8 h may help to decrease albumin-adjusted calcium. Bisphosphonates, corticosteroids, calcium chelators, or dialysis are occasionally indicated in severe cases [2,33,34,40,60,61]. Patients must be closely monitored for complications caused by aggressive diuresis, including hypokalemia, hypomagnesemia, and acute renal insufficiency [2,33,34]. However, parathyroidectomy is the only curative therapy, with a success rate of 95–98% [40,41]. To prevent the progression of systemic complications of PHPT, parathyroidectomy should be performed as soon as the patient is diagnosed. Parathyroid surgery is successful if calcium levels remain normal after 6 months [2,33,34,40,60,61].

All patients with symptomatic PHPT, significantly elevated calcium levels, kidney or bone disease, or parathyroid cancer should be considered for surgery [33,34,40,60]. In asymptomatic PHPT, parathyroidectomy is a suitable treatment for patients with no contraindications to surgery. However, the NIH's 2008 modified guidelines recommend surgery for asymptomatic patients who have a serum calcium that is >1.0 mg/dL (0.25 mmol/L) above the upper limit of normal, a CrCl of <60 mL/min, a T-score of ≤ 2.5 at any site, a previous low-trauma fracture, or an age of <50 years [2,33,34,40,59]. Conversely, Macfarlane et al. [62]

discussed the guidelines' consequences and reviewed the available data showing that patients with normocalcemic hyperparathyroidism have a low risk of progression to overt disease; however, the patients' long-term risks were not well defined. In fact, the authors found that studies to suggest that asymptomatic PHPT patients have a higher incidence of cardiovascular morbidity and mortality, which might be predicted by PTH levels. Furthermore, the authors proposed that surgery decreases fracture risk and can improve neuropsychological symptoms, and concluded that long-term, randomized, controlled trials are needed to support the safety of medical surveillance are needed to support the safety of medical surveillance and some patients' progress with time [62].

Surgical options

Either general or local anesthesia can be used for patients undergoing parathyroidectomy. Local anesthesia, via a subcutaneous injection of 1% lidocaine over the intended incision and along the anterior and the posterior borders of the sternocleidomastoid muscle, ipsilateral or bilateral, is used for patient preference or comorbidities. For complications such as technical complications or toxic reactions to lidocaine, unexpected findings, or patient discomfort, general anesthesia should be considered [40-42,60,63].

Parathyroidectomy may be performed using different techniques, and either general or local anesthesia can be used. The standard procedure for PHPT is bilateral neck exploration, performed under general anesthesia, which is the best choice for patients with inherited hyperparathyroidism or multigland disease. Subtotal parathyroidectomy (i.e., removal of 3.5 glands) or total parathyroidectomy with autotransplantation of parathyroid tissue at a distant site (e.g., the forearm or sternocleidomastoid muscle) may be performed. A transverse incision of 2–4 cm in length above the sternal notch is made, following the skin lines across the anterior neck. The tracheoesophageal groove, the paraesophageal area, the carotid sheath, and the thymus should be explored if a gland is missing. Cervical thymectomy can be performed if a gland is missing in the first surgery, but mediastinum exploration should only be performed in patients who have a gland clearly localized to the mediastinum [40,60,64].

MIP allows patients to undergo focused parathyroidectomy and has the benefits of a smaller incision, a shorter operation duration, a shorter length of hospital stay, and fewer complications; it is also more cost-effective than the standard four-gland exploration [40,43,47]. A small incision is usually made ipsilateral to the preoperative localized adenoma. MIP surgery can be performed through central or lateral neck incisions and has a 97% success rate with minimal morbidity and no procedure-specific complications. Preoperative localization is critical in this situation, because most of the neck is not explored, given the focused nature of the procedure [40,43,64-66].

In radioguided parathyroidectomy, 99mTc sestamibi is used as a radiotracer and the parathyroid adenoma is localized based on detection of the radiotracer. For intraoperative gamma detection, patients are injected intravenously with a low dose of 10 mCi 99mTc sestamibi approximately 1–2 h before the operation. For patients who receive a 20 mCi dose of 99mTc sestamibi for preoperative localization, surgery should be postponed for at least 3 days. Intraoperatively, the gamma probe can be inserted through the incision to perform radionuclide and in vivo counts based on the background count. An in vivo-to-background percentage of >150% strongly suggests a parathyroid adenoma. After excision of the identified parathyroid gland, the gland counts are measured by the top of the gamma probe while directed away from the patient to determine ex vivo counts; a count of >20% of the background suggests a parathyroid adenoma, based on the "20% rule" [66-69].

Video-guided (endoscopic) parathyroidectomy is comparable to MIP in operative success, incision length, postoperative pain, cosmetic results, and complication rates. This approach facilitates recognition of recurrent laryngeal nerve and blood vessels surrounding the parathyroid glands, but it is slower. It is contraindicated in patients with previous neck surgery, negative preoperative localization, or a large goiter, or in patients who need local anesthesia [65,69]. Video-guided parathyroidectomy can be performed by using several techniques. The anterior approach permits bilateral exploration and does not need gas insufflation [70,71]. Camera and endoscopic instruments can be used through a 10–15-mm incision just above the sternal notch [40,60,70]. The lateral approach uses camera and endoscopic instruments through one 5-mm and two 2-mm incisions near the sternocleidomastoid muscle, allowing the surgeon to visualize the glands located posteriorly in the tracheoesophageal groove. The lateral approach requires low pressures of gas insufflation of the neck to avoid significant subcutaneous emphysema [40,71]. Though technically challenging, the best approach for patients who want to avoid having neck scars is the transaxillary approach [72].

Postparathyroidectomy management

It is vital to ensure that there is no expanding hematoma in the surgical wound. Antiemetics should be used to limit nausea and vomiting, which can lead to suture dislodgement. The majority of endocrine surgeons prescribe oral calcium supplements for a few weeks or vitamin D supplements in patients with very low postoperative PTH or a high risk of postoperative hungry bone syndrome. Patients should be re-evaluated 1-2 weeks after discharge to check the surgical site and serum calcium and PTH levels. Serum calcium and PTH levels should be reassessed after 6 months to confirm cure, and then annually to ensure that they remain normal and that abnormal tissue has not regrown. A follow-up bone density test is suggested at 1 year after surgery to guide the treatment of bone loss [2,13,15,33,34,40,60].

Complications

Despite a low incidence rate of 1%, bleeding and hematoma formation are fatal complications of neck surgery, as a rapidly expanding hematoma can lead to venous congestion and airway compromise. Careful intraoperative hemostasis is vital, as well as immediate bedside evacuation with subsequent exploration and closure [73]. Temporary or permanent recurrent laryngeal nerve injury and hoarseness are caused mainly by errors surrounding the varied anatomy of the recurrent laryngeal nerve and its relationship to the thyroid gland. Although intraoperative recurrent laryngeal nerve monitoring devices may help the surgeon to identify the nerve, there are no clear data to support that the use of such devices reduces the rate of nerve injury during parathyroid surgery [74].

Transient or permanent hypoparathyroidism and hypocalcemia occur frequently after subtotal or total parathyroidectomy because of ischemic injury to healthy parathyroid gland(s). Preservation of one gland is sufficient to maintain normocalcemia. The immediate primary treatment of postoperative biochemical hypocalcemia is calcium and/or vitamin D supplementation. Appropriate patient education on the symptoms of hypocalcemia and the liberal use of calcium replacement therapy is necessary prior to discharge [75]. Parathyroid cryopreservation can be used in patients who have a high risk of severe postoperative hypocalcemia [76].

Persistent or recurrent disease has an incidence ranging from 1% to 10% [77]. Following parathyroidectomy, hypercalcemia within 6 months is defined as persistent disease and hypercalcemia after 6 months is defined as recurrent disease. Persistent or recurrent disease may be caused by surgeon inexperience, incomplete exploration, or supernumerary glands. Preoperative parathyroid surgery in these cases presents a challenge, as dense scar tissue and distorted tissue planes obscure intraoperative localization [78-80].

Special conditions in parathyroid surgery

In persistent or recurrent cases, cure rates decrease as the number of previous neck operations increases [78-80]. Thus, numerous protocols have been suggested to improve surgical outcomes in patients who require reoperation. While one proposal includes mandatory 99mTc sestamibi scanning and cervical ultrasound before the operation [78], other protocols recommend a series of CTs, MRIs, and selective venous sampling until localization is achieved [79]. Many groups have reported appropriate, safe, and effective outcomes if both accurate preoperative imaging and IoPTH are used [78]. Medial cervical incision is the standard approach, as it allow bilateral cervical exploration, although some surgeons prefer to use the lateral approach to avoid scar tissues and achieve better posterior access to the thyroid bed [78,79]. In addition, several surgeons recommend radioguided parathyroidectomy in the reoperative setting [67-69]. A video-assisted thoracic approach, median sternotomy, or partial sternal split may be needed in some cases [70,81].

In parathyroid carcinoma, the most common surgical approach is aggressive en bloc tumor resection, which includes an ipsilateral thyroid lobectomy and resection of adjacent soft tissues, perhaps including the recurrent laryngeal nerve, esophageal wall, or strap muscles if the tumor is adherent [17]. In pediatric patients, the standard of care is bilateral neck exploration; however, because data were primarily obtained from patients with PHPT resulting from single adenomas, focused parathyroidectomy is ideal to minimize scarring and postoperative complications [82,83]. In the elderly, surgery has a high cure rate, low morbidity, no mortality, and a short length of hospital stay. Surgery was found to be optimal relative to medical management when life expectancy reached 5 years for outpatients and 6.5 years for inpatients [84,85]. Finally, in pregnant women, a cervical ultrasound can be used for preoperative localization, and surgery is the treatment of choice during the second trimester [30].

Medical therapy options

In patients who are not candidates for surgery or those unwilling to undergo parathyroidectomy, treatment recommendations include annual serum calcium and creatinine testing and BMD measurement every 1–2 years. Patients should be encouraged to maintain a normal intake of calcium. Medical management includes: 1) bisphosphonates and hormone replacement therapy to decrease bone turnover and improve BMD, although they do not decrease serum calcium or PTH levels; 2) cinacalcet to reduce serum calcium and PTH levels and raises serum phosphorus levels, although it does not reduce bone turnover or improve BMD [79]. Cinacalcet reduces PTH secretion by binding the calcium-sensing receptor (CaR) of parathyroid cells [86]. In a multicenter, randomized, double-blind study evaluated the effect of cinacalcet on PHPT patients found that there were no significant changes in BMD. However, after 52 weeks of treatment normal serum calcium levels were achieved in 73% of patients, and serum PTH decreased by only 7.6% [87]. 3) Vitamin D should be measured and replaced if the pre-parathyroidectomy vitamin D level is <20 ng/mL or <50 nmol/L [88].

Ultrasound-Guided Ethanol Ablation

Ultrasound-guided ethanol ablation is an alternative therapy for PHPT in patients with MEN type 1, recurrent disease, or extreme morbidity who cannot receive surgical or medical treatment. The parathyroid tumor is localized by ultrasound and the tumor is percutaneously injected with ethanol; however, this method has a very low cure rate, requiring close follow-up of serum calcium and possibly repeat treatments [89]. Moreover, Harman et al. and Karstrup et al. reported recurrent laryngeal nerve injury in 5.6–7.1% of patients with PHPT who underwent percutaneous alcohol ablation [89,90].

Conclusion

PHPT is the most common cause of outpatient hypercalcemia. Currently, PHPT is being identified during the asymptomatic stages, due to the widespread use of screening tests; however, it is associated with high mortality due to its systemic complications. Hypercalcemia should be evaluated carefully to confirm the diagnosis, identify the cause, and rule out hereditary disorders. Many advances have been made in the diagnosis and management of this condition, but PHPT in all of its variants remains a surgically managed disease. Recurrent and persistent diseases are uncommon, but present numerous challenges. Future research is needed to identify the best treatment, minimize complications, and improve quality of life.

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Review Article Open Access

Presurgical Infant Orthopedics for Cleft Lip and Palate: A Review

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Abstract

Cleft lip and palate deformities are some of the most common facial and oral anomalies. Severe cleft forms are associated with severe nasolabial deformities, and present a significant surgical challenge in order to achieve a functional and aesthetic outcome. Presurgical infant orthopedics has been used in the treatment of cleft lip and palate for some centuries. Starting with the McNeil method, several methods and modifications had been developed by different clinicians over time. However, there is no consensus in the literature on infant orthopedic methods and their benefits. Therefore, the aim of this review is to discuss presurgical infant orthopedic methods and their advantages and disadvantages. Presurgical orthopedics allows not only the alignment of cleft segments, but also molding alar cartilages and nose tip. In addition, this procedure allows performing primary alveolar grafting or gingivoperiosteoplasty to establish a union bone at the cleft side as well. However, there have been some studies reporting that there was no positive effect of presurgical orthopedics on the maxilla and maxillary arch. There is still no consensus in the literature on the best protocol for orthopedic and surgery methods for the treatment of cleft lip and palate in infants.

Keywords: Cleft lip and palate; Presurgical infant orthopedics; Nasoalveolar molding

Introduction

Clefts of the lip and palate are some of the most common facial and oral anomalies. These anomalies can appear with considerable variation in form and severity [1]. The maxillary structure of the cleft lip and palate is divided in two or three segments by the cleft of the palate and alveolus. A unilateral cleft defect is characterized by a wide nostril base and separated lip segments on the cleft side. Severe cleft forms are associated with severe nasolabial deformities, and present a significant surgical challenge in order to achieve functional and aesthetic outcomes [2]. The affected lower lateral nasal cartilage is displaced laterally and inferiorly, resulting in a depressed dome, increased alar rim, oblique columella, and overhanging nostril apex [3]. When associated with cleft palate, the nasal septum deviates to the non-cleft side, with an associated shift of the nasal base [4]. The bilateral cleft lip and palate may be symmetrical or asymmetrical, depending on the equality of involvement on both sides. In these patients, both nasal chambers are in direct communication with the oral cavity, and the turbinates are clearly visible within both nasal cavities. The premaxilla may be small or large, and projects considerably forward from the facial aspect of the maxilla [5].

Cleft lip and/or palate patients have feeding, functioning, aesthetic, speech, and psychological problems; and therefore, are best managed through a team of experts [6]. Management of cleft lip and/or cleft palate is a process that starts in infancy and continues in adulthood. These patients undergo many surgical procedures throughout life. Numerous methods and treatment strategies have been developed over the years to reduce the number of surgeries. Despite the fact that there have been many advances in surgery, certain orthopedic corrections prior to the primary surgery are still required in patients with cleft lip and palate. For this purpose, presurgical infant orthopedics is suggested for achieving better surgical outcomes. Since it is widely accepted the intervention of multidisciplinary teams for treating cleft patients, various methods have been developed for presurgical infant orthopedics. The aim of this review is to summarize the current state of knowledge of the effects of presurgical infant orthopedics (PSIO) on long-term outcomes of different treatment protocols. In this review, the advantages, disadvantages, effects on maxillary growth, and dentoalveolar arches, as well as in speech and complications of some presurgical infant orthopedics methods will be discussed. A PubMed search was performed using the terms PSIO, presurgical nasoalveolar moulding and its long-term results and related articles were selected for the review. In addition, limitations of these studies will be discussed.

Presurgical Infant Orthopedic Methods

Some presurgical implementations in infants were developed a few centuries ago. Facial binding or adhesive tape strapping was used centuries ago to narrow clefts before surgery [7]. The use of a bonnet and strapping to stabilize the premaxilla after surgical retraction has also been reported [8]. Head is still used today to retract the premaxilla [9], and T traction using an external device has been reported as useful for surgical procedures in short-term [10]. All procedures, which at the time were mainly performed by orthodontists or by the surgeons, were based on the ever proven assumption that a narrow and well aligned cleft would be easier to repair, with less undermining and less mobilization of soft tissues. A narrower cleft would also require less tension in the repaired lip, and thus, the aesthetic outcome, facilitation of feeding, and speech was improved [11-15]. Presurgical infant orthopedics aims at securing a good maxillary arch form in an acceptable relation with the mandible, and at restoring normal oral function [7]. It also corrects angulation of the palatal shelves to a more horizontal position [16]. It is generally accepted that modern presurgical infant orthopedics started with the McNeil technique [17]. Since McNeil, many researchers have published their own methods for obtaining proper growth and development of the face, and for improving surgery results. The Hotz appliance, and then the Latham device were introduced for aligning the cleft segments [18-23]. Some authors used a combination of these appliances like in the Brogan technique, which combines the

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McNeil technique and the Hotz plate [7]. Later, Grayson and Cutting described the "presurgical nasoalveolar molding (PNAM)" concept for molding not only cleft segments but also nasal appearance [24]. Certain investigations reporting short- and long-term results of these methods mentioned above are summarized below.

Active appliances

McNeil Method: McNeil was the first in aligning presurgically the alveolar parts in cleft lip and palate patients [17]. He suggested the use of serial appliances to approximate cleft alveolar segments. By molding the palatal segments into the correct position using a series of acrylic plates, McNeil believed that this would produce a normal maxilla, while reducing the alveolar and palatal cleft at the same time. McNeil and Burston claimed that soft tissues overlying the hard palate were stimulated to grow, and they also added that neonatal maxillary orthopedics could control and modify the postnatal development of the maxilla [7]. In addition, the use of a series of acrylic plates may be favorable for patients who have to travel long distances and are unable to visit the orthodontics clinic weekly. Another advantage may be foreseeing the final position of the alignment arches.

Latham device: The other appliance used for aligning cleft segments is the Latham device, which was introduced by Dr. Latham [25-27]. In this approach, forces are applied using a pinned palatal appliance in order to manipulate mechanically the maxillary segments into close approximation, which is followed by alveoloperiosteoplasty and lip adhesion. According to Drs. Latham and Millard, these alignments allow the performance of gingivoperiosteoplasty (GPP), providing stabilization of the maxillary segments and reconstruction of the nasal floor [27]. Bercowitz et al. reported a longitudinal study in unilateral and bilateral cleft lip and palate treated with the Latham device. They also performed periosteoplasty in all cases, and compared the results to patients treated with a non-orthopedics procedure without GPP, and treated just with a lip adhesion method. They found a higher frequency of anterior and posterior crossbite in the presurgical orthopedics group [28]. Some authors have commented that those findings might be the result of the periosteoplasty procedure [7]. Dr. Latham applied the Latham device with less extensive surgery in cases of bilateral cleft lip and palate, and he assessed their dental occlusion and lateral head radiographs at 5 years of age. He found greater values for cephalometric measures in maxillary length, maxillary prominence, and ANB angle compared to previous cases [29].

In another long-term study, more anterior open bites and posterior crossbites were found in unilateral and bilateral cases compared to non orthopedics and periosteoplasty group [30]. In the study of Chan et al., in which they evaluated active appliances longitudinally, dental models of patients with unilateral cleft lip and palate (UCLP) were assessed using the Goslon Yardstick. GPP and lip adhesion were performed both in non-orthopedic and in orthopedic groups. No significant differences were found in Goslon scores between the two groups. The authors concluded that Latham procedures did not affect dental arch relations in preadolescent children with UCLP [31]. Similarly, Allareaddy et al. stated that, outcomes are predictable without any major adverse events or complications by using Latham device [32]. Besides, it was stated that Latham device could be useful in unusual cleft cases [33].

Passive appliances

Hotz appliance: The Hotz appliance, also known as the Zurich approach, in which arch alignment is achieved by grinding away the acrylic in specific areas, was introduced after the McNeil technique. Although there is no strict research about the outcomes of the Hotz plate, it was stated that this method had a tremendous impact on cleft patients [20]. According to Hotz and Gnoinski, the primary aim of presurgical orthopedics is not to facilitate surgery or to stimulate growth, as postulated by McNeil, but to take advantage of intrinsic developmental potentials. Therefore, the Zurich approach, after a lip operation is performed at the age of 6 months, palate repair is postponed until 5 years of age [22]. These authors concluded that orthopedic guidance combined with optimal timing of surgery has beneficial effects. In a study investigating the short-term effects of the Hotz plate, a harmonization in the vertical and transverse positions of the segments was found in the plate group compared to the control group [34]. In another study with 4 years follow-up of the Hotz plate group, the width of the palate was larger in the Hotz plate group than in the control group, but no difference was observed in the anteroposterior distance of the palate between the groups [13]. In addition, Sasaguri et al., investigated the long-term effects of the use of the Hotz plate and lip adhesion. They found that arch width and length of the anterior part of the maxillary were larger in the Hotz (+) group than in the Hotz and lip adhesion group, and in the group without Hotz plate and palatoplasty, at 5 years of age. The anterior part of the maxillary arch was wider in the Hotz group than in the other two groups [35]. In another long term study, Silvera et al. concluded that The two-stage palatoplasty in combination with application of the Hotz' plate had good effects on the maxillary growth than one stage palatoplasty without Hotz plate up to the age of 12 years [36].

Nasoalveolar Molding Appliance: In 1993 Grayson et al. introduced the PNAM concept, which continues to play significant role in neonatal cleft lip and/or palate treatment [24]. This approach is preferred by certain orthodontists because it produces improved results, and allows repositioning of the maxillary alveolus and surrounding soft tissues. Grayson and colleagues have reported many studies about PNAM treatment and they suggested the use of this appliance for improving nasal appearance, which results in less secondary nasal surgeries. This procedure also minimizes the need for later alveolar bone grafting, allows GPP, as well as effective retraction of the protruded premaxilla, and lengthening of the deficient columella [37,38]. In addition, produces limited maxillary growth disturbance [39]. PNAM has become very popular among orthodontists because of its nasal molding effect [40]. It is also suggested to correct septal deviation in early ages without surgery, since nasal cartilages are able to mold easily in the first postnatal 2 months because maternal estrogen provides the molding for the nasal cartilages.

In the PNAM approach the orthodontist adjusts the appliance every 1–2 weeks in 1 mm increments by removing hard acrylic resin, and adding soft acrylic resin. Once the maxillary alveolar segment gap is less than 6 mm, a nasal stent can be added to the appliance using acrylic resin placed on 0.036 inch-thick wire. The stent is positioned 3–4 mm into the nostril just below the soft tissue triangle of the nose. The size and shape of the stent is adjusted by adding soft acrylic to help create a "tissue expander" effect on the length of the cleft-side columella, as well as to reposition the malpositioned lower lateral cartilage. This process can take several months and results in a delay of the definitive cleft lip repair until approximately 4–5 months of age. PNAM should ideally begin before 6 weeks of age to take advantage of the early plasticity of nasal cartilages [18].

The first goal of PNAM in bilateral cases is to move the premaxillary segment posteriorly and medially, while preparing the lateral alveolar clefts to come in contact with the premaxilla [40]. The posterior lateral palatal shelves are molded to the appropriate width to accept the premaxilla. The premaxilla is retracted and derotated as necessary using the molding plate in conjunction with external tape and elastics. In addition, another important point is the elongation of the columella [38]. Cutting et al. stated that a saddle should be placed at the lip and columella junction. This saddle produces a separation between lip and columella that is expanded along an anterior vector, while the prolabium is stretched downwards using tape. Several months of appliance adjustments are often required. They also reported that much of the nasal tip shape produced through presurgical molding was

lost within a few weeks because of the fibroadipose tissue deposited between the widely separated nasal domes. Therefore, they suggested removing the fibro-fat tissue from between the nasal domes of the lower lateral cartilages, and suture them together in the midline without an external incision.

Grayson pointed out that multiple nasal surgical revisions are often indicated to approximate the nasal symmetry, because surgical techniques for managing nasal deformity are lacking. He also pointed out that in bilateral cleft lip and palate (BCLP), the deficient columella and ectopic premaxilla are the primary reconstructive challenges. Multiple nasal surgeries are required, which often result in excessive scarring at the columella-prolabial junction, and lack of nasal projection [41]. Therefore, he emphasized the importance of nasal molding before surgery in the early neonatal period. In addition, some other appliances for nasal molding have been reported [42]. However, the permanence of the improvement in nasal symmetry and appearance using PNAM remains controversial; however, there is a trend towards a positive effect. Liou et al. reported that nasal asymmetry was significantly improved after nasoalveolar molding in infants with cleft lip and palate; but after the primary closure of the cleft lip and nose, there was a significant relapse of the nasal asymmetry in the first year postsurgery, which remained stable afterwards. This relapse was the result of a significant differential growth between cleft and noncleft sides in the first year postsurgery [43]. Similarly, Pai et al., who used the nasoalveolar molding (NAM) appliance in their study, concluded that there was some relapse of nostril shape in width (10%), height (20%), and angle of columella (4.7%) at 1 year of age, compared to their presurgical status [44]. Therefore, the use of a nasal stent has been suggested after primary lip closure, at least for 6 months. Nonetheless, in a long-term study, it was found that the change in nasal shape is stable until early childhood, and it was emphasized that the symmetry in nose shape was maintained [45]. In another longitudinal study with 8 year follow-up, the rate of residual fistula was assessed, and it was found that NAM in conjunction with nasal floor closure contributes to a low incidence of oronasal fistulae [46]. Another longitudinal study investigating the effects of NAM approach on further surgery requirements reported that NAM-prepared patients were more likely to have less severe clefts, present the best surgical outcomes, and need less revision surgeries compared to patients not prepared with NAM [47].

The average age at the time of appliance is another concern. Grayson and Maull focused on starting neonatal period (within first one month) for better nasal esthetics results, while in the Latham technique, started within 8-11 weeks [32]. However, Shetty et al., evaluate the effects of nasoalveolar moulding (NAM) in complete unilateral cleft lip and palate infants presenting for treatment at different ages. Study groups comprised: group I treated with NAM within 1 month of age; group II treated with NAM between 1 and 5 months of age. This study concluded that the effects of NAM were most significant in group I. Group II patients also benefited from NAM, although to a lesser extent. This study validates the use of NAM in infants presenting late for treatment [48].

Limitations of Presurgical Infant Orthopedics Studies

Since cleft lip and palate treatment requires multidisplinary approaches, outcomes may be affected at any stage of treatment. Therefore, the pure effect of PSIO appliances is very difficult to assess because of the variety in timing and sequence of treatment protocols for both surgery and orthodontics. The major difficulty when comparing different presurgical orthopedic methods is the type of surgical technique, and whether performing sequential palatal closure (one or two stage) or GPP, at what age, the experience of the surgeon [49-52]. The debate on the ideal time for hard palate closure is not over so far. Furthermore, because of the different timing for gathering representative sample sizes, and the inability to obtain untreated control groups, the comparison of the effects of different orthopedic appliances is an almost impossible task. Another limitation is that previous studies, except one, have not examined the severity of clefts in infants. Peltomaki et al. found that patients with large clefts and small arch circumference, arch length, or both, showed less favorable maxillary growth than those with small clefts. Therefore, further randomized control studies comparing the effects of PSIO within different orthopedic and surgical techniques are needed for assessing long-term results [53].

Another surgical issue is completing the osseous union at the cleft region at the time of primary lip closure, which may affect maxillary growth, and therefore, influence the outcome of presurgical infant orthopedics. Different methods have been used for this purpose, and some of them, such as primary alveolar grafting, have been abandoned because of the detrimental effects on maxillary and facial growth [54-56]. As minimal invasive methods such as GPP provide bone union, there is a debate regarding the effect of the combination of this technique with presurgical infant orthopedics. Two cleft groups were compared in a study; one group underwent presurgical alveolar molding followed by GPP at the time of lip repair, while the other group did not undergo molding and GPP. The authors investigated whether narrowing of the cleft parts and GPP diminished the need for bone-grafting later. The results of this study showed that all patients in the control group required bone grafts, while 60% of patients treated with presurgical orthopedics and GPP did not need a secondary alveolar bone graft in the mixed dentition [37]. However, although these benefits have been stated by many authors, there is no consensus regarding the utility of GPP or secondary alveolar bone grafting [37]. Another issue is that most of the anterior growth of the maxilla takes place by the age of six years [57]. Similarly, Wood et al. were unable to demonstrate any clear impairment of maxillary growth in patients treated with GPP compared to patients not treated with this technique [58].

Complications

Some studies have reported complications in soft and hard tissues using PNAM therapy [59-61]. Grayson and Maull reported some problems including soft tissue breakdown, intraoral ulcerations, and failure to apply tapes and elastics, cooperation issues, and the eruption of neonatal teeth during treatment. They reported that common areas of breakdown were the frenilum attachments, the anterior premaxilla, or the posterior fauces, as the molding plate is retracted. They also reported that the intranasal lining of the nasal tip can become inflamed if too much force was applied by the upper lobe of the nasal stent [61]. The other most frequent problem was the development of cheek skin rashes [40]. In the study of Lewy-Bercowsky et al., soft and hard tissue complications were mentioned. Contact dermatitis due to repeated removal of tapes, meganostril produced by improper positioning of the nasal stent, overactivation of the nasal stent resulting in bruises or petechiae in the dome area were mentioned as soft tissue complications. Neonatal teeth eruption during treatment, or premature eruption of the incisors due to the pressure exerted by the acrylic plate, which creates a T-shape maxillary arch after the use of the molding plate, were reported as hard tissue complications [61].

In a unique study, the effects and complications of two PSIO treatment methods were compared. The authors stated that both Grayson and Figueroa nasoalveolar molding improved nasal deformities, and reduced alveolar gaps in a similar manner; however, the Figueroa technique was associated with fewer oral mucosal complications and better efficiency [62].

Opinions Against Presurgical Orthopedics

Despite the fact that the usefulness of these methods has been pointed out, presurgical orthopedic procedures have been stated as unnecessary in some studies of the Eurocleft project. One of these

studies was performed by Kuijpers-Jagtman and Prahl Andersen analyzing neonatal orthopedics of the Zurich approach, for over 20 years. According to their longitudinal observations, neonatal orthopedics is not the best approach. They conducted a randomized clinical trial named "Dutchcleft" in three centers, and compared infant orthopedics and non-orthopedics groups in relation to general, orthodontic, and cost effectiveness, as well as speech effects of these approaches. Regarding general effects, there was no difference between the groups in weight for age, length for age, or weight for length. When they assessed the maxillary arch form and dimensions, they found that cleft gap was reduced significantly in the orthopedic group; however, no significant differences were found between the groups after lip closure [7]. Furthermore, Prahl et al. found that infant orthopedics did not prevent collapse of the maxillary arch [14]. Therefore, in the Dutchcleft study there were no observable effects on occlusion and jaw relationships at the ages of 4 and 6 years [63]. Evaluation of speech and language development showed that at one year of age, children who wore plates presented an enhanced production of alveolar sounds; however, at the age of 1.5 year, when the plate was no longer used, a limited effect on speech was observed [64]. At 30 months of age, the phonologic development of the orthopedic group was normal or delayed, while most children in the non-orthopedic group presented an abnormal development [65]. Taking into account the results of the Dutchcleft trial, there is no need to perform infant orthopedics for unilateral cleft lip and palate.

Papadopoulos et al. also investigated the effectiveness of presurgical infant orthopedics using a systematic review [66]. They showed that there were no significant differences in craniofacial and dentoalveolar changes, indicating that PSIO treatment had no effect on cleft lip and palate patients. The limited evidence derived from this study does not seem to support the short- or long-term effectiveness of PSIO in these patients. Furthermore, Van der Heijden et al. performed a meta-analysis, and inferred that the results of studies on nasoalveolar molding were inconsistent in relation to changes in nasal symmetry, although there was a trend towards a positive effect [67]. In a similar manner, Uzel and Alparslan concluded in their systematic review that presurgical infant orthopedic appliances have no long-term positive effects in patients with cleft lip and palate and that more randomized controlled trials are necessary. They also added that the encouraging results on the effect of nasoalveolar molding appliances on nasal symmetry need to be supported by future randomized controlled trials [50].

Presurgical infant orthopedics has been investigated in terms of cost-effectiveness. The main principle of cost-effectiveness analysis is to estimate the cost and treatment outcome compared to an alternative treatment. The total cost of presurgical orthopedics was higher in the treatment group of the Dutchcleft study [68]. In this study, the mean medical cost for infant orthopedics treatment was US$852. The non-orthopedics treatment group had a significantly lower mean medical cost (US$304). Mean travel costs and indirect nonmedical costs were US$128 and US$231 for the orthopedics, and US$79 and US$130 for the non-orthopedics groups, respectively. However, the additional cost of neonatal maxillary orthopedics might be partly outweighed by the costs in speech therapy in later years, as the group treated with neonatal orthopedics had a significantly better rating for speech [69]. Based on the results of the Dutchcleft study, the authors concluded that neonatal maxillary orthopedics for unilateral cleft lip and palate is not necessary for feeding, patient's satisfaction or orthodontic reasons. Regarding speech, a positive but very limited effect was found until the age of 2.5 years.

Apparently, studies concerning presurgical orthopedics in cleft lip and palate have been heterogeneous and lacked adequate reporting. In particular, surgical time and sequence of surgery were stated as decisive factors for the final success, rather than the presurgical orthopedic treatment type [7]. It should be kept in mind that the best surgery approach for these patients was not described, and the outcomes were affected not only by presurgical orthopedics, but also by surgery methods [70-74]. There are many surgical alternatives as there are many type of orthopedics. Future prospective longitudinal studies are needed to achieve a consensus on the effect of presurgical orthopedics, as well as the best treatment approach.

Conclusion

It can be inferred from this review that presurgical orthopedic appliances are useful for aligning cleft segments, reducing soft tissue tension and improving nasal aesthetics. Although in some investigations it was found that there were no differences between the groups that underwent presurgical infant orthopedics and those who did not; there is a trend towards a positive effect on nasal symmetry with the use of the PNAM appliance. Assessments on the effects of different combinations of cleft surgery and orthopedics methods are still needed. Therefore multidisciplinary treatment modalities are of great importance for the rehabilitation of cleft patients.

Conflict of interests

Authors have no conflict of interests to disclose.

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Research Article
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Prospective Analysis of Patients with Axillary, Palmar and Axillary-Palmar Hyperhidrosis who Underwent Bilateral R4-R5 Video-Assisted Thoracoscopic Sympathicotomy

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Abstract

Background: Video-assisted thoracoscopic sympathicotomy is a safe, effective and minimally invasive procedure, and its emergence greatly changed hyperhidrosis treatment. However, the possibility of standardizing interruption levels on the sympathetic chain has not yet been evaluated. This study sought to evaluate the frequency of compensatory sweating and the recurrence and satisfaction rates after bilateral R4-R5 video-assisted thoracoscopic sympathicotomy in patients with primary focal hyperhidrosis with involvement of the axillary, palmar, or both regions.

Methods: From November 2010 to February 2013, an observational prospective cohort study was conducted with 42 patients who underwent bilateral video-assisted thoracoscopic sympathicotomy. During the procedure, electrocautery was performed along the sympathetic chain at the levels R4-R5, and the nerve of Kuntz and the path between levels R4-R5 were also sectioned.

Results: No cases in which the video-assisted thoracoscopy had to be converted to thoracotomy were observed. Compensatory sweating was observed in 47.6% of patients within the first six months after surgery, decreasing to 30.9% at the end of this period. Hyperhidrosis recurrence occurred in only two patients. In total, 24.1% of patients with associated plantar hyperhidrosis reported that the condition disappeared after surgery. The satisfaction rate was 89.7% in the immediate postoperative period.

Conclusions: The frequency of compensatory sweating, the recurrence rate of symptoms and the satisfaction rate after sectioning by cauterization with electrocautery at the R4-R5 levels were similar to those reported for other types of interruption and other levels studied. Moreover, the interruption level adopted also had beneficial effects on plantar hyperhidrosis.

Keywords: Hyperhidrosis; Surgery; Sympathectomy; Electrocautery

Introduction

Hyperhidrosis is defined as a pathological condition of excessive sweating in amounts greater than physiologically necessary for thermoregulation, and this condition can be classified as primary or secondary [1,2] and as focal or generalized. Focal hyperhidrosis is idiopathic and occurs more frequently in the palmar, plantar, axillary, inframammary, inguinal, and craniofacial regions [1,2]. The incidence of primary focal hyperhidrosis varies in different geographical areas and populations [3,4]. Women are generally more involved than men by this condition, and higher prevalence rates occur in adolescents and young adults [3,4]. Although no studies have described the natural course of the disease relative to age, Haider et al. [1] reported that the intensity of symptoms decreases in patients over 50 years of age.

The pathophysiology of hyperhidrosis is not entirely known, but it is accepted that hyperactive sweat glands are a result of exaggerated stimulation of the sympathetic autonomic nervous system. The eccrine glands are responsible for focal hyperhidrosis and are affected by emotional and gustatory stimuli. Although eccrine glands play a primary role in hyperhidrosis, some researchers believe that both eccrine and apocrine glands may have equal participation in axillary hyperhidrosis [5,6].

There are several ways to treat hyperhidrosis, including the use of topic antiperspirants, iontophoresis, anticholinergics, beta-blockers, benzodiazepines, and botulinum toxin. However, clinical treatment options are not very satisfactory and have high recurrence rates [1,3]. Conversely, surgical treatment with sympathectomy (resection of part of the sympathetic chain) or sympathicotomy (sectioning of levels of the sympathetic chain) is currently considered the method of choice [2]. The main side effects of sympathectomy include reflex or compensatory sweating, bradycardia, Horner's syndrome, chylothorax, hemothorax, pneumothorax, intercostal neuralgia, and recurrence [4].

Clinical history and physical examination are important tools to indicate the most appropriate individualized therapy in patients with hyperhidrosis. There are a number of clinical treatments for hyperhidrosis, including topical therapy, iontophoresis, systemic therapy, and botulinum toxin. Aluminum chloride and aluminum chlorohydrate salts are the most common topical treatments [7,8]. In addition to its limited effectiveness, the common side effects of topical

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treatments (including burning sensation and local irritation) may reduce the benefits of treatment. A further alternative is iontophoresis, which has been reported to be effective in individuals that have both palmar and plantar hyperhidrosis. Iontophoresis requires long term use to maintain efficacy, necessitating home treatment; furthermore, this procedure is contraindicated in pregnant women, patients with a pacemakers or large metal prostheses, and who suffers from epilepsy [9,10]. The use of oxybutynin, an anticholinergic oral medication, is limited by the frequent presence of side effects, such as dry mouth, headache, constipation, and urinary retention. This type of treatment would, however, be suitable in cases which do not respond to topical treatments, botulinum toxin, or iontophoresis [11,12]. Botulinum toxin is effective, safe and has good tolerability as an alternative to topical, systemic, and surgical treatments; however, because primary hyperhidrosis is a chronic condition, questions about longevity of treatment efficacy remain [7,9]. When clinical options do not offer satisfactory results, a variety of surgical procedures can be used, including localized and thoracic surgery. Located surgery can only be used to treat axillary hyperhidrosis [7]. Although effective in resolving symptoms, this procedure often requires the placement of drains and is associated with a number of complications and side effects, including infection, hematoma, necrosis, atrophic or hypertrophic scarring, alopecia, and hyperpigmentation [7,13].

The emergence of video-assisted thoracoscopic sympathicotomy greatly changed hyperhidrosis treatment, and this procedure is safe, effective, and minimally invasive [14,15]. In this procedure, the sympathetic chain is interrupted by sectioning or ablation of the nerve using electrocautery, a harmonic scalpel, or surgical clips. Despite the increasingly frequent use of video-assisted thoracoscopic sympathicotomy, evaluation of its long-term impact has been limited. Aiming to standardize this procedure, we believe that interrupting the sympathetic chain at the R4-R5 level in patients with hyperhidrosis in different regions may provide similar results as other types of interruption and other levels studied thus far. Therefore, the present study sought to evaluate the frequency of compensatory sweating and the recurrence and satisfaction rates after bilateral R4-R5 video-assisted thoracoscopic sympathicotomy in patients with primary focal hyperhidrosis with involvement of the axillary, palmar, or both regions.

Materials and Methods

Patient population

From November 2010 to February 2013, an observational prospective cohort study was conducted with 42 patients with primary focal hyperhidrosis (axillary, palmar or axillary-palmar). These patients underwent bilateral video-assisted thoracoscopic sympathicotomy with sectioning by cauterization with electrocautery along the sympathetic chain at the R4-R5 levels.

The criteria used to diagnose primary focal hyperhidrosis included focal sudoresis with visible and excessive sweating for a period ≥ 6 months with no known clinical or drug cause combined with at least one of the following [6]: bilateral symmetrical disease; frequency of at least one episode per week; interference with daily activities; onset of symptoms before 25 years of age; family history of hyperhidrosis; and cessation of sweating during sleep.

In the preoperative period, all patients underwent a rigorous evaluation of their clinical history, electrocardiogram, and chest radiograph. The following were considered as contraindications for the procedure: secondary hyperhidrosis, body mass index ≥ 28 kg/m^2, heart rate <60 bpm, and radiological sequelae of pulmonary disease with probable signs of pleuropulmonary adhesions. After the surgical procedure, patient follow-up was performed during the first 24 hours, on days 15 and 30 and in the sixth month of the postoperative period, when the onset of compensatory sweating and/or recurrence of symptoms were evaluated, in addition to patient satisfaction. Compensatory sweating was classified based on the classification proposed by Atkinson et al. [16] as follows: absent (patient does not develop any new sweating in other areas); mild (patient develops new mild sweating in other areas, but it does not bother the patient); moderate (patient develops new sweating in other areas, but the patient still desires treatment); and severe (patient develops new sweating so serious that the patient regrets having undergone the procedure).

According to the World Medical Association Declaration of Helsinki, the study protocol was approved by the Research Ethics Committee of the State University of Rio de Janeiro, and written informed consent was obtained from all participants.

Surgical procedure

The procedure was performed with patients under general anesthesia. In some patients, orotracheal intubation was performed using a Robertshaw double lumen endobronchial tube (Broncho-Cath Left, Mallinckrodt Medical, Ireland), and in other patients, a simple tube with low-volume ventilation or small periods of apnea combined with carbon dioxide insufflators (maximum pressure of 8 to 10 mmHg at a flow rate of 8 L/min) were used. Patients were then positioned in a semi-sitting supine position with a 45-degree slope and with the upper limbs extended at a 90-degree angle relative to the body. An inframammary incision of approximately 1.5 cm was made in the anterior axillary line at the sixth intercostal space, followed by blunt dissection with penetration of the pleural cavity, and a 10-mm trocar was placed to introduce a rigid 30-degree, 10-mm optic (Karl-Storz, Tuttlingen, Germany) coupled to a miniature video camera (DX CAM Karl-Storz, Tuttlingen, Germany) to inspect the cavity and identify the sympathetic chain. Another incision of approximately 5 mm was made in the axillary region at the second intercostal space for placing a 5-mm trocar to introduce a hook clamp (Abbott Spine, Bordeaux, France) in the thoracic cavity with the aid of the rigid 30-degree optic. When the thoracic sympathetic chain was identified, a segment was sectioned by cauterization with electrocautery at the R4-R5 levels, as well as the path between levels R4-R5 and the nerve of Kuntz, whenever visualized. After the end of the procedure, a Levine tube (14 French) was introduced and water-sealed, and the lungs were expanded with Valsalva maneuvers until the air leak stopped. Then, the tube was removed with the lung in forced inspiration. The subcutaneous plane was closed with 2-0 polyglactin sutures, and the skin was closed with 4-0 polyglactin sutures. Subsequently, the same procedure was performed on the contralateral side. After the end of the procedure, patients were extubated and then underwent chest radiography for investigation of possible pneumothorax.

Statistical analysis

Descriptive statistics were used to analyze the data. The results were expressed as the median (minimum and maximum values) or number (percentage). Data analysis was performed using SAS 6.11 software (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 42 patients studied, 61.9% were female, and the median age was 23.9 years at the time of surgery (ranging from 14 to 53 years). Before surgery, axillary, palmar and axillary-palmar hyperhidrosis was diagnosed in 4, 17, and 21 patients, respectively. Twenty-nine patients (69%) complained of associated plantar hyperhidrosis.

All patients showed satisfactory results in the immediate postoperative period and on the first postoperative day, with dry hands and axillae. No cases of death related to surgery or cases in which the video-assisted thoracoscopy had to be converted to thoracotomy were

observed. The median time spent in surgery was 40 minutes (ranging from 34 to 46 minutes), and the median hospitalization time was 3 days (ranging from 2 to 5 days). In the immediate postoperative period, one patient developed pneumothorax, and another patient showed mammary hypoesthesia.

Compensatory sweating was observed in 20 (47.6%) patients within the first six postoperative months. Of these, 13 patients considered the compensatory sweating as mild, 3 as moderate, and 4 as severe. The following regions had the highest occurrence of compensatory sweating: trunk (8), thighs (6) and generalized form with involvement of the trunk, thighs, and buttocks (2). The onset of compensatory sweating was observed most often between days 15 and 30 of the postoperative period in 12 (60%) of the 20 patients.

Regarding the initial area affected by hyperhidrosis before surgery, we observed that compensatory sweating appeared in the axillary region of 2 (50%) of the 4 patients with axillary hyperhidrosis. Compensatory sweating appeared in the palmar region of 7 (41.2%) of the 17 patients with palmar hyperhidrosis and in the axillary-palmar region of 11 (52.4%) of the 21 patients with axillary-palmar hyperhidrosis.

At the end of the sixth month after surgery, 7 patients reported that the compensatory sweating had disappeared, whereas 9 did not report any improvement, although the clinical manifestations no longer bothered these patients. However, 4 patients complained that the compensatory sweating was more intense and uncomfortable, with no improvement. Among the 29 patients who had preoperative plantar hyperhidrosis associated with hyperhidrosis in other areas, 7 (24.1%) reported that the plantar hyperhidrosis disappeared after surgery.

Of the 42 patients who received surgery, only 2 experienced hyperhidrosis recurrence. These subjects were initially included among the 4 patients who developed generalized and severe compensatory sweating and whose condition had not improved. In these patients, the recurrence began between the first and the sixth month after surgery, with progressive worsening during this time interval.

The satisfaction rate with the procedure was 89.7% in the first month and 76.9% in the sixth month. Among all the patients who received surgery, 89.7% reported they would recommend the surgical procedure to other patients with the same disease.

Discussion

The present study evaluated surgical interruption of the sympathetic chain segment at the R4-R5 levels in patients with axillary, palmar, or axillary-palmar hyperhidrosis, and the results were similar to those reported for other types of interruption and for other levels studied. In addition, the interruption level adopted in the present study also showed beneficial effects on plantar hyperhidrosis. To the best of our knowledge, this study is the first to demonstrate the possibility of standardizing a level for sectioning the sympathetic chain for surgical treatment of hyperhidrosis in different regions.

A wide array of therapies is available for the treatment of hyperhidrosis. It has been recommended that mild axillary hyperhidrosis is initially treated topically with aluminum salts or oxybutynin systemic therapy [9,17,18]. Botulinum toxin should be the second-line therapy in cases that do not respond to topical and systemic therapies [17]. In severe cases of axillary hyperhidrosis, botulinum toxin and topical aluminum chloride are first-line therapies [17]. The local axillary surgery should be considered after failure of other treatment options and before undergoing the patient to endoscopic thoracic surgery. Liposuction-curettage successfully relieves hyperhidrosis and, by virtue of the suctioning mechanism, may be superior to curettage alone for lasting results [9,19]. Surgical procedures are effective, safe, and permanent options for treating hyperhidrosis. Sympathectomy or sympathicotomy is advocated for debilitating hyperhidrosis of the extremities not responding to less invasive modalities [20]. However, these alternatives are reserved for severe cases, since they can have permanent side effects such as compensatory sweating [20].

In the present study, a segment of the sympathetic chain was interrupted by cauterization with electrocautery, and the path between levels R4-R5 and the nerve of Kuntz were sectioned. The most important factor related to this procedure was complete separation of the nerve as well as the space between the severed ends to prevent nerve regeneration. However, the level used for sympathetic sectioning remains controversial. In the present study, we used the Lin-Telaranta classification [21] to define specific section levels, in which the R3 and/or R4 sections were proposed for palmar hyperhidrosis, and the R4 or R4-R5 sections were proposed for patients with axillary symptoms [21]. We chose to interrupt levels R4-R5 in all patients with axillary, palmar, and axillary-palmar complaints.

Considering that the purpose of hyperhidrosis surgery is to improve the patient's quality of life, complications should be minimal or preferably eliminated. In this sample, no cases of death resulting from surgery or cases in which video-assisted thoracoscopy had to be converted to thoracotomy were observed. The postoperative complications included pneumothorax and mammary hypoesthesia, which occurred in only two patients. This further highlights the success of the selected sympathetic chain interruption levels, and our results indicate the possibility of using the R4-R5 levels as a standard in all patients with axillary, palmar, and axillary-palmar symptoms.

Compensatory sweating is the most common adverse effect of sympathectomy, and its occurrence may vary between 3 and 98% [22,23], with an average frequency of 60% described in the literature [24]. In some cases, the manifestation of this condition is transient and resolves after 6 to 12 months, although chronic cases may reach 67% according to Gossot et al. [24]. In the present study, 30.9% of patients remained with this complication after six months of follow-up, whereas 16.7% of patients reported the disappearance of compensatory sweating at the end of the sixth-month follow-up period. Regarding severe compensatory sweating, the frequency reported in the literature varies but was shown to reach 36% of cases in one report [25]. However, according to Montessi et al. [26], the frequency of severe compensatory sweating may vary depending on the level sectioned, with rates of 32% after cauterization at the R2 level, 9% after cauterization at the R3 level, and only 4% after cauterization at the R4 level. In the present study, only 4 of the 42 patients reported severe compensatory sweating.

The hyperhidrosis recurrence rate after video-assisted thoracoscopic surgery reported in the literature varies between 0% and 65% [27,28]. In the present study, it was observed that only two patients experienced hyperhidrosis recurrence; one patient had an initial complaint of axillary hyperhidrosis, and the other complained of axillary-palmar hyperhidrosis. The recurrence rates reported in the literature for focal axillary hyperhidrosis vary between 15 and 65% [24,29], whereas the overall recurrence rate of palmar hyperhidrosis varies between zero and 16% [30]. However, it is important to investigate whether such case are related to the presence of secondary hyperhidrosis, so that the possible causes of recurrence can be identified. Interestingly, Lin et al. [31] found that the causes for recurrence were neural regeneration in 18.8% of cases, incomplete disruption of the R2 node in 12.5% of cases and integrity of the nerve of Kuntz in 18.8% of cases.

Previous studies including a series of patients treated with sympathectomy for primary hyperhidrosis showed a high degree of patient satisfaction. In our study, the satisfaction rate was 89.7% in the first month and 76.9% in the sixth month after surgery. We believe that this reduction in the satisfaction rate during the follow-up period may be attributed to the emergence of compensatory sweating and/or

recurrence. In the literature, the best results were reported by Cohen et al. [32], with a satisfaction rate of 98.2%. Surprisingly, in the present study, 24.1% of patients with complaints of plantar hyperhidrosis associated with hyperhidrosis in other areas reported that the plantar abnormality disappeared after surgery. This finding was also reported by Gossot et al. [24], who found that 15% of patients described an improvement in plantar-associated symptoms, and some patients were even considered cured after the procedure.

A critical analysis of the results and their limitations is important. The present study was conducted with a small number of patients and only investigated the interruption of the sympathetic chain at the R4-R5 levels. Furthermore, we evaluated only subjects with axillary, palmar, or palmar-axillary hyperhidrosis. Despite these limitations, our results suggest that it is possible to standardize the levels for sectioning the sympathetic chain for surgical treatment of hyperhidrosis in different regions. We believe that the present study represents an important contribution to the field because it may serve as a starting point for future clinical trials with greater numbers of patients and other sympathetic chain interruption levels.

In conclusion, the present study shows that bilateral video-assisted thoracoscopic sympathicotomy at the R4-R5 levels is a safe procedure that provides good results in the treatment of primary focal hyperhidrosis with axillary, palmar and axillary-palmar involvement. The frequency of compensatory sweating, the recurrence rate of symptoms and the satisfaction rate found for sectioning by cauterization with electrocautery at the R4-R5 levels were similar to those previously reported in the literature for other types of interruption and other levels studied. Moreover, the sympathetic chain interruption levels used in the present study also showed beneficial effects on plantar hyperhidrosis.

Conflict of Interest

The authors have no conflict of interest to report.

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Research Article Open Access

Conversion Rate to Resectability in Colorectal Cancer Liver Metastases: Need for Criteria Adapted to Current Therapy.

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Abstract

Background: Therapeutic strategy for patients with colorectal cancer liver metastases (CRLM) is based on good monitoring and correct assignment to classes of liver resectability based on imaging criteria, taking into account the surgical risk.

Objective: To identify the post-treatment time frame for confirming resectability (conversion to resecability) or permanent unresectability.

Methods: The study is a prospective analysis based on a Scientific Protocol (Surveillance of patients with colorectal cancer liver metastases) used in the Ist Surgical Oncology Unit, Regional Institute of Oncology Iaşi, Romania. Surgical treatment, oncologic treatment, response to therapy , postoperative surgical complications, were assessed at 3, 6 and 9 months after start of the study.

Results: In the interval July 2012 - January 2014, 106 patients were diagnosed with CRLM. According to the classes of liver resectability the patients were divided into four groups: group I (clear resectability), group II (possibly resectability), group III (susceptible resectability), group IV (unresectable metastases). Relevant for the study were only groups II and III. Thus, in group II patients the rate of conversion to resectability was 23.07% and in group III patients 26.66%. These results were obtained after 3, 6 and 9 months of therapy, respectively.

Conclusions: Rigorous surveillance of patients with CRLM according to a well-established scientific protocol, and their assignment to liver resectability classes represent the first step ofthe oncosurgical therapeutic strategy. An improvement in the rate of conversion to resectability could be achieved through regular assessment of treatment response based on international criteria that should include besides the number and size of target lesions the post-therapy morphological tumor changes.

Keywords: Colorectal liver metastases; Colorectal cancer; Onco-surgical strategy; Conversion to resectability; Resectability criteria; Therapeutic response criteria

Abbreviation: CRLM: Colo-Rectal cancer Liver Metastases; LMs: Liver Metastases; CRC: Colo-Rectal Cancer; CRR: Conversion to Resectability Rate; ADPT: Absolute Disease Progression Time Interval; ADPR: Absolute Disease Progression Rate

Introduction

Colorectal cancer is the third most common cancer worldwide among men (incidence 21 per 100,000 and mortality rate 10 per 100,000) and the second among women (incidence 15 per 100,000 and mortality rate 8 per 100,000). In Central and Eastern Europe, the incidence is 35 per 100,000 men and 22 per 100,000 women and mortality rate 20.3 per 100,000 men and 11.7 per 100,000 women. The overall 5 year survival rate is 50-60% [1].

These rather disappointing results are mainly due to (remote) secondary lesions that most commonly affect the liver. Liver metastases occur in approximately 50% of all patients with CRC and represent the main cause of death. They are present in 15-25% of patients at the time of diagnosis [2-4].

Despite the recent progress in the multi-disciplinary treatment for stage IV CRC, the 5-year survival is only 6% However, the survival rate has improved considering that 10 years ago, stage IV CRC was associated with a 5-year survival of less than 1% [5].

Surgical treatment – the resection of metastases – remains the only curative treatment for CRLM. The complete resection of all liver metastases improves the overall survival from 25% (R1) to 40% (R0) [4,6]. Granting all this, the relapse / recurrence rate after curative liver resections remains high, ranging from 50% to 70% [7].

These fluctuations in survival rate are mainly related to the selection of the indications for liver resection. The benefits are due to the imaging techniques, which offer a better choice of surgical procedures. Also, the development of other complementary techniques (portal vein embolization, thermoablation) and oncological therapies (chemotherapy, molecular therapy) have increased patient eligibility

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for resection of liver metastases (LMs). Currently, 25-30% of all patients with CRC and liver metastases may benefit from liver resection [8,9]. It has been proved that for patients with synchronous LM who received both pre and post-op chemotherapy, there was a significantly increased percentage of survival, without escalation of the neoplastic disease [10]. The median survival rate for patients with untreated colorectal LMs ranges between 4.5 and 15 months; patients who survived 5 years were also recorded.

The monitoring of surgically treated CRC patients (with or without LMs) was analyzed by randomized prospective studies, which showed an absolute reduction rate of 10% in the 5-year mortality rate. The early identification of a relapse, which is possible under a strict surveillance, results in an average survival increase of 8.5 months, compared with the absence of such surveillance [11,3].

Intensive surveillance is associated with a higher rate of resectability for metastases (76% *vs* 56%), the diagnosis of smaller liver metastases (3 cm *vs* 4 cm) and an improved survival rate (26.8% *vs* 12.5% at 3 year survival) [12,13].

Material and Method

Patients

This study represents an 18 months prospective analysis based on surveillance protocols of patients with liver metastases of colorectal cancer, which was used in the First Surgical Clinic of the Regional Institute of Oncology (IRO) Iași, Romania. The origin of this protocol is a classification of patients into 4 groups of resectability of liver metastases: clearly resectable, possibly resectable, susceptible resectable and unresectable metastases (Table I). Inclusion criteria:

Age: over 18 years

- Pathology: diagnosis of colorectal carcinoma
- Imaging diagnosis: (CT / MRI) of liver metastases
- Signed informed consent
- Accepts to follow exactly the treatment proposed by the Oncologic Committee of IRO

Exclusion Criteria:

Age: under 18 years

Diagnosis of rare colorectal cancer (sarcoma, lymphoma, melanoma, endocrine tumors, carcinoid tumor)

Cancer with particular location (anal canal, appendix)

Does not fully accept the treatment proposed by the Oncologic Committee of IRO

Diagnosis

The clinical diagnosis was made by the surgeon treating the patient and confirmed by a second, independent surgeon. The diagnosis was confirmed after the analysis of the results of the following investigations: morpho-pathology of the primary tumor (biopsy or resection piece), colonoscopy, imaging (abdominal CT / MRI), radiology (chest X-ray +/- chest CT), and immunology (CEA: Carcino Embryonic Antigen).

Tumor staging was done according to the 7th edition of TNM stage criteria for colorectal cancer provided by the American Joint Committee on Cancer (AJCC). The criteria for classifying the patients into the 4 groups are shown in Table 1 [14].

Treatment

In order to better standardize the study, the surgical interventions were divided into:

Interventions on the primary tumor

Curative resection (right or left colectomies, total colectomies, anterior rectal resections, abdomino-perineal rectum excisions, Hartmann procedures);

Palliative interventions (digestive bypass colostomy).

Interventions on liver metastases

Minor liver resections (≤ 3 liver segments);

Major liver resections (> 3 liver segments).

Complementary interventions ("adjuvant")

Local therapy (thermoablation, portal vein ligature, port-a-cath insertion into the hepatic artery);

Complementary oncological interventions (excision of lymph node recurrences, peritoneal biopsy, liver biopsy, loco-regional lymphadenectomy - usually associated with major resections);

Interventional radiology procedures (hepatic portal vein embolization and chemoembolization artery).

Associated interventions

Represent interventions for keeping a radical intervention (block

Tabel I: The criteria for classifying patients into study groups [14].

Study groups	Criteria for patient assignment to
Group I – CLEAR resectabilityn=27 (25.47%)	- maximum 3 unilateral LMs, away from vessels
	- resection of maximun 4 liver segments
	- at least 40% remaining liver parenchyma
	- normal functional status of remaining liver parenchyma
	- absence of extrahepatic metastases
Group II – POSSIBLY resectabilityn=13 (12.26%)	- LMs with vascular contact
	- need for complex, extended resection
	- 25-30% remaining liver parenchyma
	- normal functional status of remaining liver parenchyma
	- absence of extrahepatic metastases
Group III – SUSCEPTIBLE resectabilityn=15 (14.15%)	- multiple, bilateral LMs, but with a clear unilateral predominance
	- insufficient functional status of remaining liver parenchyma
	- possible but resectable extrahepatic metastases
Group IV - UNRESECTABLE metastastasesn=51 (48.11%)	- multiple, bilateral LMs
	- presence of unresectable extrahepatic metastases
	- unresectable primary tumor, recurrence, or contined primary tumor progression (imaging or bioptic confirmation)

resection) or interventions without any influence on the development of neoplastic disease (hysterectomy, Hartmann's reversal, enterectomy, appendectomy, cholecystectomy, inguinal hernia surgical repair, surgical repair of incisional hernia).

For patients with a resectable primary tumor and resectable synchronous LMs (clearly or possibly resectable) the therapeutic approach was as follows:

- Simultaneous resection (primary tumor and liver metastases), possible in primary tumors that are relatively easily resectable (right colon, sigmoid and less in rectal cancer) associated with minor hepatectomy (≤ 3 resected liver segments); preferable when the duration of surgery and intraoperative incidents (bleeding) do not affect the patient's postoperative recovery;

- Staged resection (primary tumor resection without liver metastases approach, but with intent to be removed after cancer treatment); it is used especially in cases where the patient's condition does not allow for another surgical sequence.

For patients with an unresectable primary tumor and resectable synchronous LMs, the surgical treatment was palliative (colostomy, digestive bypass) without resection of the liver metastases. The "Liver first approach" strategy (a reversed treatment sequence in which the CRLM are resected before the primary carcinoma) was not used. The therapeutic options for each group are listed in Table 2.

For thermoablation of the LMs an ultrasonic generator system was used (SonoSurg G2). Hepatic artery chemoembolization (Seldinger technique) and portal vein embolization (trans-parietal) were performed at the Radiology Unit of the "Sf. Spiridon" Hospital, Iasi, Romania.

Curative chemotherapy (neo-adjuvant, induction, and adjuvant) and palliative chemotherapy were administered according to the guidelines suggested by the NCCN (National Comprehensive Cancer Network). First line chemotherapy consisted in one of the regimens shown in Table 3. After the first tumor progression the regimen was changed (second-line chemotherapy). After the second tumor progression, the regimen was once again changed (third line chemotherapy) or a palliative treatment was initiated, depending on the patient's general condition and their tolerance to chemotherapy. Palliative or symptomatic treatment was initiated after the third tumor progression.

Although not generally agreed on by all oncologists, this division of chemotherapy as "neo-adjuvant", "induction", and "adjuvant" helps to assess the treatment response in terms of goal and expectation. It is argued that neo-adjuvant chemotherapy is administered to patients

Tabel II: Therapeutic options by study group.

Study groups	Onco-surgical options
Group I	• primary tumor resection and LMs resection simultaneous or staged (synchronous LMs)
	• resection of metachronous LMs
	• port-a-cath insertion into the hepatic artery
	• systemic neoadjuvat chemothrapy (after primary tumor resection - in patients with synchronous LMs pending „hepatic sequence")
	• systemic +/- locoregional adjuvat chemotherapy (after LMs resection – simultaneous with primary tumor ressection in patients with synchronous LMs or in patients with metachronous LMs)
	• monoclonal antibody targeted therapy (anti-EGFR, anti-VEGF)
Group II	• primary tumor resection and staged LMs resection (synchronous LMs)
	• resection of metachromous LMs (depending on the opporunity of a major hepatectomy)
	• port-a-cath insertion into the hepatic artery
	• systemic neoadjuvant chemotherapy (after primary tumor resection – in patients with synchronous LMs pending „hepatic sequence")
	• systemic +/-locoregional adjuvat chemotherapy (after LMs resection - in patients with metachromous LMs)
	• monoclonal antibody targeted therapy (anti-EGFR, anti-VEGF)
	• reassessment of the opportunity of LMs resection depending on the response to treatment
Group III	• primary tumor resection (synchronous LMs)
	• port-a-cath insertion into the hepatic artery
	• thermoablation (only if is possible for all LMs from one liver lobe, in association with portal vein embolization / ligature)
	• portal vein embolization / ligature
	• hepatic arterial chemoembolization
	• systemic induction chemotherapy (in patients with metachronous LMs or in patients with synchronous LMs following primary tumor resection)
	• monoclonal antibody targeted therapy (anti-EGFR, anti-VEGF)
	• reassessment of the opportunity of LMs resection depending on the response to cancer treatment
Group IV	• primary tumor resection (synchronous LMs and resectable primary tumors)
	• digestive bypass or colostomy (synchronous LMs and unresectable primary tumors)
	• port-a-cath insertion into the hepatic artery
	• hepatic arterial chemoembolization
	• systemic palliative chemotherapy
	• monoclonal antibody targeted therapy (anti-EGFR, anti-VEGF)

Table III: Protocol of chemotherapy for metastatic colorectal cancer*.

Chemotherapy regimens	Posology
Capecitabine +/- bevacizumab or cetuximab	- capecitabine 850-1250 mg/m2 po twice daily, days 1-14
	Repeat every 3 weeks
	- bevacizumab 7.5 mg/kg iv, day 1
	- cetuximab 500 mg/m2 iv, over 2 hours, day 1
	(KRAS/NRAS WT gene only)
FOLFOX +/- bevacizumab or cetuximab	- oxaliplatin 85 mg/m2 iv, over 2 hours, day 1
	- leucovorin 400 mg/m2 iv, over 2 hours, day 1
	- 5-FU 400 mg/m2 iv bolus day 1, then 1200 mg/m2 /day×2days iv continuous infusion
	Repeat every 2 weeks
	- bevacizumab 5 mg/kg iv, 1 day, every 2 weeks
	- cetuximab 500 mg/m2 iv, over 2 hours, day 1, every 2 weeks (KRAS/NRAS WT gene only)
CapeOX +/- bevacizumab or cetuximab	- oxaliplatin 130 mg/m2 iv, over 2 hours, day 1
	- capecitabine 850-1000 mg/m2 twice daily po for 14 days
	Repeat every 3 weeks
	- bevacizumab 7.5 mg/m2 iv, 1 day, every 2 weeks
	- cetuximab 500 mg/m2 iv, over 2 hours, day 1, every 2 weeks (KRAS/NRAS WT gene only)
FOLFIRI +/- bevacizumab or cetuximab	- irinotecan 180 mg/m2 iv, over 30-90 minutes , day 1
	- leucovorin 400 mg/m2 iv, infusion to match duration of irinotecan, day 1
	- 5-FU 400 mg/m2 iv bolus day then 1200 mg/m2 /day×2days iv continuous infusion
	Repeat every 2 weeks
	- bevacizumab 5 mg/m2 iv, 1 day, every 2 weeks
	- cetuximab 500 mg/m2 iv, over 2 hours, day 1, every 2 weeks (KRAS/NRAS WT gene only)
IROX	- oxaliplatin 85 mg/m2 iv, over 2 hours, followed by
	- irinotecan 200 mg/m2 iv, over 30-90 minutes , day 1
	Repeat every 3 weeks
FUFOL (5-FU/LV)	- leucovorin 500 mg/m2 iv, over 2 hours, weekly, 6 weeks
	- 5-florouracil (5-FU) 500 mg/m2 iv, bolus 1 hour after start of leucovorin, weekly, 6 weeks
	Repeat every 8 weeks

*NCCN Guidelines.

with tumors considered resectable, therefore optional but recommended. Induction chemotherapy is administered to patients with borderline resectable or unresectable tumors, so it is a therapy of necessity, its goal being tumor "downsizing" and “downstaging” to resectability.

Assessment of Treatment Response

According to the scientific surveillance protocol, CRLM patients should be assessed at the time of admission (study entry) and every 3 months for the first 2 years , then every 6 months for the next 3 years - based on clinical examination, chest Xray +/- chest CT, abdominal CT/ MRI, ACE. Colonoscopy should be done every 2 years or when suspecting (clinically or by imaging) a primary tumor recurrence. We considered as patients "lost from follow-up" those who did not come back as scheduled for their surgical / oncological reassessment, without being able to confirm the death of the patient, or those who waived the treatment proposed by the Oncology Commission. The rationale behind performing evaluations every 3 months is that this period corresponds roughly to 3 cycles of chemotherapy (the average number of chemotherapy cycles for CRLM, after which any imaging changes can be noticed) .

The imaging evaluation of therapeutic response was based on the abdominal CT, interpreted using RECIST criteria. For all the investigations, baseline evaluation and follow-up, we used the same imaging protocol with the following scanning parameters:

- Native scan (pre-contrast scan) biphasic approach after intravenous contrast injection (arterial and portal phase) using bolus triggering for CT Siemens 16 slice or test injection for CT Philips Brilliance 6 slice;

- Effective section width (ESW) was less than or equal to 5 mm, and remained constant at all assessments (baseline and follow-up);

- Continuous sections of 3/3 mm, 4/4 mm or 5/5mm;

- Intravenous contrast: iodine concentration 370 mg/ml, amount 1.2 ml/kg, flow rate 3-4 ml/s;

- oral contrast prior to examination 500 ml over 30 minutes before the examination (only for liver examination), 1000-1500 ml over 60 minutes before the examination (only for abdominal-pelvic examination);

- Rectal contrast - between 500 - 1000 - 2000 ml if the examination of the rectum and colon was also intended;

- Scanned volume includes the lungs apices to the pubis symphysis or above the diaphragm to the pubis symphysis. The used RECIST criteria are shown in Table 4 [15].

Statistical Interpretation

The data for the study was collected from the IRO Iasi electronic system, the patient surgery protocols and the medical records in the IRO Iasi archives. The database was processed in MS Excel, and statistical analysis was performed using RStudio software. Student t test, Pearson-χ^2, Fisher exact test, and ANOVA tests were used. Significance threshold was $p < 0.05$.

For this study we defined three notions:

1. Conversion to resectability rate (CRR)

$$CRR = \frac{\text{patients in groups II+III who became resectable}}{\text{total number of patients in groups II+III}}$$

2. Absolute disease progression time interval (ADPT)

Table IV: RECIST criteria*.

Therapeutic response	Size and number imaging criteria
Complete Response (CR)	- disappearance of all target lesions
	- any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	- at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	- at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study); in addition tothe relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm
	- the appearance of one or more new lesions
Stable Disease (SD)	- neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

*RECIST Working Group guideline (version 1.1)

ADPT = [from study enrollment, to the date when the patient became unresectable]

3. Absolute disease progression rate (ADPR)

$$ADPR = \frac{\text{patients in groups II+III who became unresectable}}{\text{total number of patients in groups II+III}}$$

The aim of this study was to evaluate CRR, ADPT, and ADPR. Also, this study is trying to demonstrate the need for a surveillance protocol of patients with CRLM.

Results

Between June 1, 2012 and December 31, 2013, there were 106 patients admitted at the First Surgical Oncology Unit of IRO Iasi with CRLH diagnosis, which met the inclusion criteria into the study. These patients were divided into 4 groups according to the criteria shown in Table 1, each group representing a class of liver metastases resectability.

The general characteristics of patients (age, sex), comorbidities (interpreted by ASA score and Charlson Comorbidity Index Risk) and staging of the primary tumor based on the analysis of morpho-pathology report are shown in Table 5.

The average age of the statistical community was 63.17 years (range 37-90). The distribution of the patients along the 4 groups was relatively homogeneous with regard to their age; the ANOVA test does not reveal any significant difference in this regard (F=0.624, p=0.60).

Of all the patients included in the study, 63.21% (n=67) were men and 36.79% (n=39) women. The Fisher test does not indicate a significant dependence between the group type and the gender of the patients (p=0.3915).

Not all patients had associated diseases; 11 patients did not present any comorbidity. Analysis of associated disorders revealed a large number of cardiovascular diseases (n=108) followed at a distance by digestive diseases (n=43). The identified oncologic diseases included: synchronous cancer (colon) in 2 patients, metachronous cancers (breast, colon, ovarian, mesenteric) in 4 patient, and local tumor recurrences in 5 patients.

There was a very strong association between the study groups and life expectancy expressed as Charlson Comorbidity Index (p=0.0002639). A strong dependence was found between resectability classes and anesthetic risk expressed as ASA Score (p=0.01062).

Analysis of morpho-pathology reports for the primary tumors revealed only one T1case in group II, the remaining cases presenting a high degree of local invasion and being relatively evenly distributed: 49 patients (46.23%) with tumors exceeding the muscularis propria (T3) and 56 patients (52.83%) with tumors exceeding the visceral peritoneum and / or invading the neighboring organs (T4a, b). In almost half of the patients (n=45, 42.45%), metastases were found in less than 3 lymph nodes (N1). The dominant tumor grade was G2 (moderately differentiated) being observed in 41 patients (38.68%). These are summarized in Table 5.

Carcinoembryonic antigen (CEA) is a marker of first choice for colorectal cancer and was collected from all study patients before treatment. CA 19-9 is a marker of first choice for pancreatic cancer, but may be high in colorectal cancer and was also collected from all study patients before treatment. The levels of the two tumor markers in the four study groups are shown in Table 6.

Chest X-rays were routinely performed for all patients, both for detection of pulmonary metastases and for the preoperative evaluation of the patient, even though not included in RECIST. Thus 14 patients (13.2%) with lung metastases were identified; in 2 cases, presenting a probable resectability of lung metastases, the performed chest CT infirmed the resectability of lesions.

Abdominal CT showed that LMs were most frequently multiple and bilobar (n=26), followed by those located in segment VIII (n=16), as seen in Table 7. Fisher's exact test indicates statistically significant differences between the number of LMs in each segment and the 4 study groups for liver sections IVa, IVb, V, VI, and VII. A total volumetric assessment of LMs and normal healthy liver parenchyma was not possible in every patient.

The therapeutic characteristics, response to treatment, and postoperative complications (according to Clavien-Dindo classification) for all 4 study groups are presented in Tables 7-11.

Apparently difficult to analyze, Tables 7-11 must be interpreted from the initial surgical and oncological treatment to the 3 month treatment response, and, based on this response, follow on to the interpretation of the treatment performed. Therefore, in a column can be followed the treatment response during the last 3 months; according to this response the treatment for the next 3 months is established. Notes with explanations (a-s) are the same for all tables VII - XI and are found at the end of the table XI.

After dividing the patients into study groups it was found that only 25.47% of patients (group I) were eligible for safe liver resection and 48.11% (group IV) were not candidates for curative treatment.

Data analysis for the entire statistical collectivity highlights the following aspects:

Surgical procedures with curative intent on primary tumor for 55 patients, palliative surgery for 14 patients; five patients were inoperable and 32 patients had primary tumor resection in their history;

Complementary interventions were performed to 59 patients;

Associated interventions were performed to 24 patients;

Liver resections were performed in 34 patients (15 major + 19 minor), accounting for 32.07% of all patients; of these, 7 patients (6.66%) with possible or susceptible resectability were converted to resectability

Table V: Patients and tumor characteristics.

Variables	Lot I n=27 (25.47%)	Lot II n=13 (12.26%)	Lot III n=15 (14.15%)	Lot IV n=51 (48.11%)	Total n=106	p-value
Age (mean)	60.96	63.69	66.06	63.37	63.17	**(ANOVA) 0.6**
Gender						
Male	19	10	10	28	67	**(Fisher) 0.3915**
	70.37%	76.92%	66.66%	54.90%	63.21%	
Female	8	3	5	23	39	
	29.62%	23.07%	33.33%	45.09%	36.79%	
ASA Score						
I	8	1	6	10	26	**(Fisher) 0.01062**
	29.62%	7.69%	40.00%	19.60%	24.52%	
I	16	10	7	19	54	
	59.25%	76.92%	46.66%	37.25%	50.95%	
III +	3	2	2	22	26	
	11.11%	15.38%	13.33%	43.14%	24.52%	
Charlson Comorbidity Index						
6	4	1	6	11	22	**(Fisher) 0.0002**
	14.81%	7.69%	40.00%	21.56%	20.75%	
7	18	3	1	28	50	
	66.66%	23.07%	6.66%	54.90%	47.17%	
8 +	5	9	8	12	34	
	18.52%	69.23%	53.33%	23.53%	32.07%	
pTNM-stage						
T1	0	1	0	0	1	**(Fisher) 0.0031**
		7.69%			0.94%	
T2	0	0	0	0	0	
T3	16	8	10	15	49	
	59.25%	61.53%	66.66%	29.41%	46.23%	
T4a,b	11	4	5	36	56	
	40.74%	30.76%	33.33%	70.59%	52.83%	
N0	6	0	0	11	17	**(Fisher) 0.2473**
	22.22%			21.57%	16.03%	
N1	11	6	7	21	45	
	40.74%	46.15%	46.66%	41.17%	42.45%	
N2	10	7	8	19	44	
	37.03%	53.84%	53.33%	37.25%	41.51%	
G-grading						
G1	9	0	2	4	15	**(Fisher) <0.0001**
	33.33%		13.33%	7.84%	14.15%	
G2	9	8	3	21	41	
	33.33%	61.54%	20.00%	41.17%	38.68%	
G3	7	5	7	20	39	
	25.93%	38.46%	46.66%	39.22%	36.79%	
G4	2	0	0	6	8	
	7.40%			11.76%	7.55%	
Gx	0	0	3	0	3	
			20.00%		2.83%	

Table VI: Levels of ACE and CA 19-9 markers.

Variables		Group I	Group II	Group III	Group IV	p-value (ANOVA)
ACE	minimum	1.28	1.05	1.86	2.1	0.471
	maximum	958	1487	2220	6331	
	mean value	66.95	208.66	376.01	422.45	
	standard deviation	211.47	487.79	706.57	1154.09	
CA 19-9	minimum	0.6	2.78	6.61	0.85	0.117
	maximum	325.9	273.3	95.82	2695	
	mean value	49.87	63.7	41.25	310.8	
	standard deviation	76.6	91.95	31.27	611.96	

Table VII: Main CT characteristics of hepatic metastases.

	Group I	Group II	Group III	Group IV	Total	p-value (Fisher)
Number of LMs						
LMs limited to 1 segment						
I	0	0	0	3	3	0.8213
II	1	3	1	3	8	0.1753
III	0	2	1	2	5	0.0973
IVa	2	6	2	0	10	<0.0001
IVb	3	4	1	0	8	0.0013
V	6	4	3	0	13	0.0002
VI	7	4	3	0	14	0.0001
VII	6	3	3	0	12	0.0004
VIII	6	4	3	3	16	0.0295
LMs limited to 2 segments	0	0	1	6	7	0.2399
LMs limited to 3 segments	0	0	1	5	6	0.2998
Multiple, bilobar LMs	0	0	4	22	26	<0.0001
Size of LMs						
minimum	6 mm	7 mm	5 mm	5 mm	5 mm	n.a.
maximum	38 mm	38 mm	95 mm	78 mm	95 mm	n.a.

Table VIII: Treatment, therapeutic response and postoperative surgical complications in group I 27 patients (19 synchronous LMs + 8 metachronous LMs.

Variables	Baseline evaluation	At 3 months	At 6 months	At 9 months
Surgical Treatment				
Primary tumor				
curative intent resection[a] (simultaneous + staged)	12+7 (70.37%)	n.a.	n.a.	n.a.
palliative interventions[b]	0 (0.0%)	n.a.	n.a.	n.a.
previous resection[c]	8 (29.62%)	n.a.	n.a.	n.a.
Liver metastases				
minor resection[d]	13 (48.14%)	3 (11.11%)	3 (11.11%)	0 (0.0%)
major resection[e]	7 (25.92%)	0 (0.0%)	1 (3.70%)	0 (0.0%)
positive resection margins	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Complementary interventions[f]	11 (40.74%)	2 (7.40%)	2 (7.40%)	2 (7.40%)
Associated interventions[g]	10 (37.03%)	0 (0.0%)	4 (14.80%)	0 (0.0%)
Unoperated patients[h]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oncological Treatment				
neoadjuvant chemotherapy[i]	7 (25.92%)	4 (14.80%)	0 (0.0%)	0 (0.0%)
adjuvant chemotherapy[j]	20 (74.06%)	23 (85.18%)	27 (100%)	27 (100%)
induction chemotherapy[k]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
palliative chemotherapy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
molecular therapy[l]	2 (7.40%)	11 (40.74%)	12 (44.44%)	12 (44.44%)
Treatment Response				
RECIST[m]				
partial response[n]	n.a.	2 (7.40%)	4 (14.80%)	0 (0.0%)
complete reponse[o]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
stable disease	n.a.	25 (92.59%)	23 (85.18%)	27 (100%)
progressive disease	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Site of tumor progression				
primary tumor[p]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Liver[r]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Extrahepatic[s]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
mixed	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-surgical mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Postoperative Surgical Complications (Clavien–Dindo Classification)				
Grade I	13 (48.14%)	0 (0.0%)	1 (3.70%)	0 (0.0%)
Grade II	8 (29.62%)	2 (7.40%)	1 (3.70%)	0 (0.0%)
Grade III	2 (7.40%)	0 (0.0%)	1 (3.70%)	0 (0.0%)
Grade IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade V(postoperative mortality)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table IX: Treatment, therapeutic response and postoperative surgical complications in group II 13 patients (11 synchronous LMs + 2 metachronous LMs).

Variables	Baseline evaluation	At 3 months	At 6 months	At 9 months
Surgical Treatment				
Primary tumor				
curative intent resection[a]	11 (84.61%)	n.a.	n.a.	n.a.
palliative interventions[b]	0 (0.0%)	n.a.	n.a.	n.a.
previous resection[c]	2 (15.38%)	n.a.	n.a.	n.a.
Liver metastases				
minor resection[d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
major resection[e]	0 (0.0%)	0 (0.0%)	3 (23.07%)	0 (0.0%)
positive resection margins	n.a.	n.a.	0 (0.0%)	n.a.
Complementary interventions[f]	8 (61.53%)	0 (0.0%)	1 (7.69%)	2 (15.38%)
Associated interventions[g]	2 (15.38%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unoperated patients[h]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oncological Treatment				
neoadjuvant chemotherapy[i]	11 (84.61%)	6 (46.15%)	0 (0.0%)	0 (0.0%)
adjuvant chemotherapy[j]	0 (0.0%)	0 (0.0%)	3 (23.07%)	3 (23.07%)
induction chemotherapy[k]	2 (15.38%)	6 (46.15%)	3 (23.07%)	0 (0.0%)
palliative chemotherapy	0 (0.0%)	1 (7.69%)	7 (53.84%)	10 (76.92%)
molecular therapy[l]	3 (23.07%)	3 (23.07%)	3 (23.07%)	3 (23.07%)
Treatment Response				
RECIST[m]				
partial response[n]	n.a.	0 (0.0%)	2 (15.38%)	0 (0.0%)
complete reponse[o]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
stable disease	n.a.	6 (46.15%)	3 (23.07%)	5 (38.46%)
progressive disease	n.a.	7 (53.84%)	8 (61.53%)	8 (61.53%)
Site of tumor progression				
primary tumor[p]	n.a.	0 (0.0%)	1 (7.69%)	1 (7.69%)
Liver[r]	n.a.	6 (46.15%)	6 (46.15%)	5 (38.46%)
Extrahepatic[s]	n.a.	1 (7.69%)	1 (7.69%)	1 (7.69%)
Mixed	n.a.	0 (0.0%)	0 (0.0%)	1 (7.69%)
Non-surgical mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Postoperative Surgical Complications (Clavien – Dindo classification)				
Grade I	4 (30.76%)	0 (0.0%)	2 (15.38%)	0 (0.0%)

Table X: Treatment, therapeutic response and postoperative surgical complications in group III 15 patients (13 synchronous LMs + 2 metachronous LMs).

Variables	Baseline evaluation	At 3 months	At 6 months	At 9 months
Surgical Treatment				
Primary Tumor				
curative intent resection[a]	13 (86.66%)	n.a.	n.a.	n.a.
palliative interventions[b]	0 (0.0%)	n.a.	n.a.	n.a.
previous resection[c]	2 (13.33%)	n.a.	n.a.	n.a.
Liver Metastases				
minor resection[d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
major resection[e]	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (26.66%)
positive resection margins	n.a.	n.a.	n.a.	0 (0.0%)
Complementary interventions[f]	12 (80%)	5 (33.33%)	0 (0.0%)	4 (26.66%)
Associated interventions[g]	2(13.33%)	0 (0.0%)	0 (0.0%)	1 (6.66%)
Unoperated patients[h]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oncological Treatment				
neoadjuvant chemotherapy[i]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
adjuvant chemotherapy[j]	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (26.66%)
induction chemotherapy[k]	14 (93.33%)	10 (66.66%)	7 (46.66%)	2 (13.33%)
palliative chemotherapy	0 (0.0%)	4 (26.66%)	7 (46.66%)	8 (53.33%)
molecular therapy[l]	4 (26.66%)	5 (33.33%)	5 (33.33%)	5 (33.33%)
Treatment Response				
RECIST[m]				
partial response[n]	n.a.	1 (6.66%)	1 (6.66%)	0 (0.0%)
complete reponse[o]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
stable disease	n.a.	9 (60%)	6 (40%)	6 (40%)
progressive disease	n.a.	4 (26.66%)	7 (46.66%)	8 (53.33%)

Site of tumor progression				
primary tumor[p]	n.a.	1 (6.66%)	1 (6.66%)	1 (6.66%)
Liver[r]	n.a.	1 (6.66%)	3 (20%)	4 (26.66%)
Extrahepatic[s]	n.a.	2 (13.33%)	1 (6.66%)	1 (6.66%)
Mixed	n.a.	0 (0.0%)	2 (13.33%)	2 (13.33%)
Non-surgical mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Postoperative Surgical Complications (Clavien – Dindo classification)				
Grade I	4 (26.66%)	0 (0.0%)	0 (0.0%)	2 (13.33%)
Grade II	4 (26.66%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade III	2 (13.33%)	0 (0.0%)	0 (0.0%)	2 (13.33%)
Grade IV	2 (13.33%)	0 (0.0%)	0 (0.0%)	1 (6.66%)
Grade V(postoperative mortality)	1 (6.66%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

without positive resection margins on morpho-pathological evaluation; only 4 of the 7 patients received molecular therapy;

There was no complete response at 9 months;

A partial response to treatment was obtained in 8 patients (7.55%), only 2 of them (1.88%) in groups II and III; no partial or complete response was obtained in any group IV patients;

Signs of progressive disease were found in 45 patients (42.45%), none in group I;

There were 12 recorded deaths (11.32%) out of which 9 were non-surgery related (8.49%) and 3 (2.83%) post-surgery; the latter resulted from septic complications after primary tumor approach (colostomy necrosis, anastomotic fistula, pelvic abscess); there has been no recorded death following the liver resections.

Although the patients characteristics, as well as the primary tumor's and LMs' characteristics were analyzed in all 4 study groups, relevant to this study were only groups II (possible resectability) and III (susceptible resectability), whose therapeutic and post-therapeutic characteristics are shown in Tables 9 and 10.

While combining the results for groups II and III, the resulting rate of conversion to resectability (CRR) is 7/28 patients (25%) after 9 months. The absolute disease progression time interval (ADPT) is 3 months for 11 patients, 6 months for 4 patients and 9 months for 1 patient. The absolute disease progression rate (ADPR) is the 5/28 patients (17.85%) at 3 months, of 14/28 patients (50%) at 6 months and 18/28 patients (64.28%) at 9 months.

Discussions

The identification of a scientific protocol based on standard diagnosis and treatment criteria and particularly the standard treatment response assessment criteria is the goal for any multidisciplinary team involved in the treatment and management of patients with CRLM.

Two decades ago, patients with unresectable liver metastases were treated with systemic chemotherapy, no other therapeutic options being considered even when there was a good response to chemotherapy. Currently, the periodic reassessment of patients receiving adjuvant treatment and the extended indications for liver resection lead to improved outcomes in terms of survival [5]. Hence it can be concluded that all goals of therapeutic strategies converge on increasing the proportion of patients that may benefit from hepatic resection. The use of "adjuvant" techniques can determine an increase in the rate of conversion to resectability of liver metastases by liver morphological changes reflected by:

Decrease in volume of liver metastases

Increase in volume of healthy liver parenchyma

A consensus conference in 2006 defined three criteria to be observed in a liver resection, regardless of its magnitude [16]:

- Complete R0 resection with a safety margin ≥ 1 cm (gold standard), but a safety margin <1 cm is not a contraindication for resection;

- Preservation of at least 2 adjacent segments with an adequate vascular inflow and outflow (portal and arterial blood supply, venous drainage) and biliary drainage;

- Adequate volume of the remaining liver (more than 20% for a healthy liver).

In this study, the criteria for assigning patients to a study group overlap some liver resectability classes. These criteria are based exclusively on imaging results without taking into account the comorbidities and surgical risk.

The statistically significant differences between the study groups on one hand and associated conditions (Charlson Comorbidity Index, p=0.0002) and anesthetic risk (ASA score) on the other hand, show that the group distribution of patients is directly correlated with life expectancy.

Statistical interpretation (Fisher test) of the data obtained after the analysis of the pathology results for the primary tumor, as an important prognostic factor, indicates significant study group variations in terms of the degree of primary tumor local invasion T (p=0.0031). Thus it can be stated that patients with primary tumors exceeding the visceral peritoneum and or invading neighboring organs (T4a,b) have or will develop forms of local or distant recurrences (hepatic and extrahepatic) generally categorized as unresectable. Statistically significant results (p<0.0001) were also obtained for the G-degree of tumor differentiation. Based on these data it can be stated that the degree of tumor differentiation has an influence on the development of local or distant recurrence (hepatic and extrahepatic); poorly differentiated, aggressive tumors, will develop hepatic or extrahepatic metastases sooner, categorized as unresectable. In contrast, no significant variations were found in the number of invaded lymph nodes, N, (p=0.2473), so this study could not demonstrate a correlation between the number of lymph nodes invaded and the resectability class of liver metastases.

The analysis and interpretation of the results, obtained by statistical processing of the data related to tumor marker levels (CEA and CA19-9), showed no statistically significant differences between the study groups. Although visually the data indicate an increasing trend of CEA levels in relation to the study groups, the ANOVA test showed statistically insignificant study group differences (F=0.851, p=0.471), accounted for by the high variance in CEA levels within the study groups. For the CA19-9 marker, the ANOVA test also indicates, at a significance level of 0.05, that the differences between study groups are not statistically significant (F=2.037, p=0.117). This may be due to the high variation of tumor markers in small study groups. CA19-9 marker had an unexpected "behavior". Thus in group III its levels were lower than in group II. This marker being a derivative of the Lewis blood group

Table XI: Treatment, therapeutic response and postoperative surgical complications in group IV 51 patients (31 synchronous LMs + 20 metachronous LMs).

Variables	Baseline evaluation	At 3 months	At 6 months	At 9 months
SURGICAL TREATMENT				
Primary tumor				
curative intent resection[a]	12 (23.52%)	n.a.	n.a.	n.a.
palliative interventions[b]	14 (27.45%)	n.a.	n.a.	n.a.
previous resection[c]	20 (39.21%)	n.a.	n.a.	n.a.
Liver metastases				
minor resection[d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
major resection[e]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
positive resection margins	n.a.	n.a.	n.a.	n.a.
Complementary interventions[f]	9 (17.64%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Associated interventions[g]	11 (21.56%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unoperated patients[h]	5 (9.80%)	5 (9.80%)	5 (9.80%)	5 (9.80%)
ONCOLOGICAL TREATMENT				
neoadjuvant chemotherapy[i]	0(0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
adjuvant chemotherapy[j]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
induction chemotherapy[k]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
palliative chemotherapy	49 (96.07%)	49 (96.07%)	48 (94.11%)	41 (80.39%)
molecular therapy[l]	16 (31.37%)	16 (31.37%)	15 (29.41%)	12 (23.52%)
TREATMENT RESPONSE				
RECIST[m]				
partial response[n]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
complete reponse[o]	n.a.	0 (0.0%)	0 (0.0%)	0 (0.0%)
stable disease	n.a.	22 (43.13%)	21 (41.17%)	10 (19.60%)
progressive disease	n.a.	27 (52.94%)	27 (52.94%)	31 (69.78%)
Site of tumor progression				
primary tumor[p]	n.a.	2 (3.92%)	2 (3.92%)	1 (1.96%)
Liver[r]	n.a.	3 (5.88%)	2 (3.92%)	4 (7.84%)
Extrahepatic[s]	n.a.	16 (31.37%)	15 (29.41%)	17 (33.33%)
Mixed	n.a.	6 (11.76%)	8 (15.68%)	9 (17.64%)
Non-surgical mortality	0 (0.0%)	0(0.0%)	1 (1.96%)	7 (13.72%)
POSTOPERATIVE SURGICAL COMPLICATIONS (Clavien – Dindo classification)				
Grade I	16 (31.37%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade II	17 (33.33%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade III	3 (5.88%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade IV	2 (3.92%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade V(postoperative mortality)	2 (3.92%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

n.a. - not applicable

a - right or left colectomies, total colectomies, anterior rectal resections, abdomino-perineal rectum excisions, Hartmann operations

b - digestive bypass, colostomy

c - for patients with metachronous LMs

d - segmentectomies (≤ 3 liver segments), metastasectomies, "wedge resection"

e - liver resection > 3 liver segments

f - locoregional lymphadenectomy (usually associated with major resections), excision of lymph node recurrences, termoablation, portal vein ligature, port-a-cath insertion into hepatic artery, peritoneal biopsy (classic / laparoscopic approach) liver biopsy (classic / laparoscopic approach); here were also included the interventional radiology techniques (portal vein embolization and hepatic artery chemoembolization)

g - hysterectomy, Hartmann's reversal, enterectomy, appendectomy, cholecystectomy, inguinal hernia surgical repair, surgical repair of incisional hernia

h - for patients unoperated after enrollment in the research

i - performed in patients with resectable LMs, after resection of primary tumor, pending liver sequence

j - systemic and / or locoregional administration in all patients who underwent liver resection

k - administered in patients with probable or likely resectable LMs, pending surgical sequence

l - targeted monoclonal antibodies (cetuximab, bevacizumab)

m - Response Evaluation Criteria in Solid Tumors

n - at least a 30% decrease in the sum of diameters of target lesions

o – disappearance of all target lesion

p – recurrence or tumor continues to progress

r – number and size assessment

s - lung, peritoneal, retroperitoneal, ovarian, bone

Table XII: Main criteria for therapeutic response assessment.

Response criteria (target lesions)	Complete Response (CR)	Partial Response (PR)	Progressive Disease (PD)	Stable Disease (SD)
WHO[1]	- 100% decrease in cross-product	- ≥ 50% decrease in cross-product	- > 25% increase from maximum response	- < 50% decrease to ≤ 25% increase in cross-product
RECIST[2]	- disappearance of all target lesions - any pathological lymph nodes reduction in short axis to <10 mm.	- ≥ 30% decrease in the sum of longest diameters (baseline sum diameters).	- > 20% increase in the sum of diameters (the smallest sum on study) + absolute increase of at least 5 mm - the appearance of one or more new lesions	- neither sufficient shrinkage to qualify for PR or sufficient increase to qualify for PD
EASL/EORTC[3]	- 100% decrease in amount of enhancing tissue	- ≥ 50% decrease in amount of enhancing tissue	- > 25% increase in amount of enhancing tissue and / or new enhancement	- < 50% decrease in amount of enhancing tissue
mRECIST[4]	- disappearance of any intratumoral arterial enhancement	- ≥ 30% decrease of the baseline sum of the diameters of viable portions (enhancement on arterial phase)	- ≥ 20 % of the smallest sum of the diameters of viable portions since the start of treatment (nadir)	- all other variations - neither response or progression
PERCIST[5]	- no metabolic activity	> 30% reduction in activity from baseline and decrease 0.8 SUL unit	>30% incrase in activity / new lesion - if doubt verify with another method (CT)	- does not meet the criteria for CR, PR, or PD
Choi[6]	- disappearance of all lesions - no new lesions	- > 10% decrease in size (sum of longest diameters) or > 15% decrease in density (HU)	- > 10% increase in size (sum of longest diameters) without reduction in density (HU) - new lesions	- does not meet the criteria for CR, PR, or PD
SACT[7]	**Favorable response**	**Unfavorable response**	**Indeterminate**	
	no new lesion and any of the following: 1. Decrease in tumor sizea of ≥ 20% 2. Decrease in tumor sizea of ≥ 10% and ≥ half of the non-lung target lesions with ≥ 20 HU decreased mean attenuation 3. One or more non-lung target lesions with ≥ 40 HU decreased mean attenuation	any of the following: 1. Increase in tumor sizea of ≥ 20% 2. New metastases or new enhancement	- does not fit criteria for favorable or unfavorable reponse	
MASS[8]	**Favorable response**	**Unfavorable response**	**Indeterminate**	
	no new lesion and any of the following: 1. Decrease in tumor sizea of ≥ 20% 2. One or more predominantly solid enhancing lesions with marked central necrosis or marked decreased attenuation (≥ 40 HU)	any of the following: 1. Increase in tumor sizea of ≥ 20% in the absence of marked central necrosis or marked decreased attenuation 2. New metastases or new enhancement	- does not fit criteria for favorable or unfavorable reponse	

1 - World Health Organization

2 - Response Evaluation Criteria for Solid Tumors - Working Group (version 1.1)

3 - European Association for the Study of the Liver / European Organization for Research and Treatment of Cancer

4 - Modified Response Evaluation Criteria for Solid Tumors

5 - Positron Emission tomography Response Criteria in Solid Tumors (version 1.0)

6 - Choi Haesun et al.

7 - Size and Attenuation Computed Tomography

8 - Morphology, Attenuation, Size, and Structure

system, 5-8% of the people (Lewis negative phenotype) are unable to synthesize it; it might be possible that some patients in group III have a Lewis negative phenotype, thus explaining the unexpected "behavior". CA19-9 is less sensitive than CEA and does not offer additional useful information for the monitoring of colorectal cancer after curative resection compared to CEA, according to some studies [17,18]. Also, it has been demonstrated that there is a correlation between CEA level and the stage of disease, without influencing the therapeutic decision and in particular the indication of adjuvant therapy [19-22]. After a R0 resection of the primary tumor and/or liver metastases, CEA level returned to normal within 4-6 weeks. A persistently high level of this marker is indicative of local residual tumor or metastases.

Statistical analysis of the data on the number of LMs and liver segments where they were located revealed a significantly different correlation between the number of LMs in each involved liver segment and the number of cases in each study group. In other words, there is a dependency between the involved liver segments (number and location) and patient assignment to a study group (assessed resectability). Patients with liver metastases in segments IVa, IVb, V, VI, VII, some of them more easily surgically approachable, were in groups I, II and III. Most common LMs were multiple, bilobar (n=16), and in this case the patients were in group IV, as shown in Table 7.

Evaluated in several studies, the rate of conversion to resectability of CRLM ranges from 13%, 33% to 41% [23-25]. In our study CRR was 25 %, a value that sits in between the data found in literature. This case highlights the lack of superiority of CRR to some studies that used a similar protocol surveillance, but their data were obtained for relatively small study groups. An interesting result is that all patients were finally redistributed as resectable and definitely unresectable after 9 months from the initial assessment. In fact, after 9 months of taking part in the study, all patients in groups II and III were categorised (Figures 1 and 2). In these groups 1 death was recorded, 2 patients, although showing signs of stable disease, were classified as unresectable due to comorbidities and the high surgical risk for a major hepatectomy.

There were significant differences between the CRR even for patients under a rigorous surveillance protocol [23-25]. These differences may result from different appreciations of the indication for liver resection. The indication for liver resection is established by the surgical team, which should take into account two factors:

- General health status of the patient (comorbidities and anesthetic risk);

- Therapeutic response evaluation.

Perhaps the most important step in the surgical oncology strategy for CRLM patients is the therapeutic response evaluation (at baseline and at well-established intervals) with reconsideration of liver resection. The most widely used criteria for treatment response assessment is RECIST (Response Evaluation Criteria In Solid Tumors). These are imaging criteria and consist of initial examination prior to treatment and dynamic (baseline and follow-up) evaluation of CT/MRI images (not by chest X-ray or abdominal ultrasound) and evaluates only the size and number of target lesions without considering the morphological changes of target lesions. PET-scan^{18}FDG (fluoro-deoxy-glucose positron emission tomography) can be used to confirm/refute the appearance of one or more new lesions. RECIST criteria were created simplistic, arbitrary, for clinical trials studying the efficacy of chemotherapy in hepatocellular carcinoma being subsequently adopted in practice. RECIST criteria are not adapted to the mechanisms of action of angiogenesis inhibitors (anti-VEGF antibody, bevacizumab), molecular therapy used since 2004 in patients with metastatic CRC. Anti-angiogenic agents (anti-VEGF) do not destroy cancer cells and do not have a direct cytocidal effect, as conventional chemotherapeutic agents, but prevent the development of peritumoral vascular micronetwork thereby limiting tumor growth, having a cytostatic effect. The combination chemotherapy + anti-angiogenic agents appear to be an optimal anti-cancer treatment, but the classical evaluation criteria (CT/MRI) cannot capture changes in morphology. Therefore, these biological agents do not have a direct effect on tumor volume, and a simple CT / MRI scam may underestimate the response to treatment.

A short meta-analysis showed that there are numerous criteria to assess therapeutic response in oncological diseases, some of them adapted to current therapy and technology. Studies in which these criteria have proven their usefulness and contribution to survival or quality of life were designed for a specific neoplastic disease, but later applied to other neoplastic diseases. Most therapeutic response assessment criteria have been created to monitor the effectiveness of one anti-cancer agent in phase II and III studies. WHO (World Health Organization) criteria and RECIST (Response Evaluation Criteria in Solid Tumors) are mainly focused on the evaluation on anatomic tumor response and were initially used for hepatocellular carcinoma.

EASL / EORTC criteria (European Association for the Study of the Liver / European Organization for Research and Treatment of Cancer) assess tumor enhancement also in hepatocellular carcinoma. mRECIST (modified Response Evaluation Criteria for Solid tumors) criteria differ from RECIST as they measure tumor enhancement as a biomarker of tumor viability. PERCIST criteria (Positron Emission Tomography Response Criteria in Solid tumors) use a metabolic assessment of the tumor tissue rather than by recording of a decrease in anatomic size. Choi criteria described by Choi Haesun et al. for the assessment of therapeutic response in gastrointestinal stromal tumors (GIST) consider both target lesion size and its density expressed in Hounsfield units. Smith AD et al. have developed criteria for assessing the progression of liver metastases of renal origin called SACT (vfgtgrwhich were modified by the same team a year later into MASS (Morphology, Attenuation, Size, and Structure) [26-39]. Key features of therapeutic response assessment criteria are shown in Table 12.

In a study conducted by a multidisciplinary team under the direction of L. Rubbia-Brandt in 196 patients with CRLM the post-

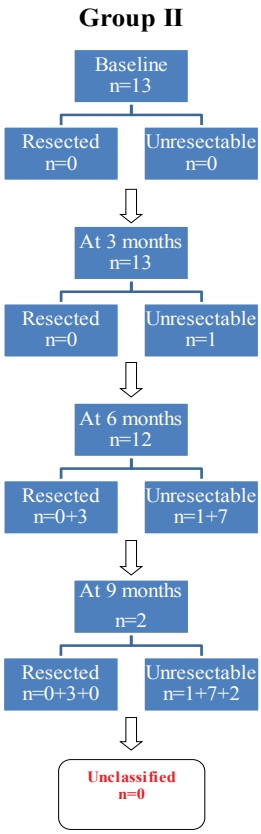

Figure 1: The pacients redistribution after 9 months of baseline evaluation (group II).

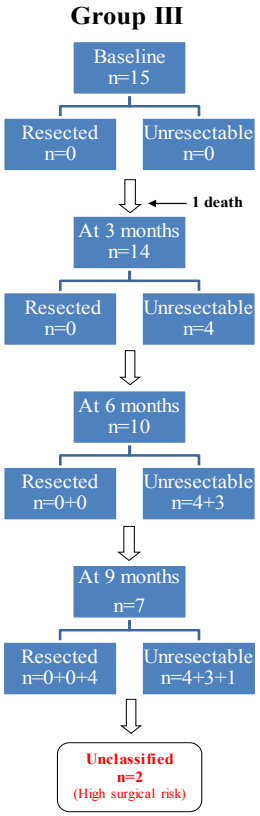

Figure 2: TThe pacients redistribution after 9 months of baseline evaluation (group III).

terapeutic response was evaluated based on morphopathological analysis of resection specimen. A tumor regression score (TRG) was used and a correlation between this score and overall survival was found. This score identifies five levels of tumor regression and is based on the presence of residual tumor and extent of fibrosis. For CRLM, the occurrence of fibrosis is correlated with a favorable response to chemotherapy and not with the occurrence of areas of tumor necrosis [40].

A muldidisciplinary team from The University of Texas, MD Anderson Cancer Center, led by D. Ribero assessed the therapeutic response based on a morphopathological analysis of resection specimens. One hundred five patients with CRLM who received induction chemotherapy + bevacizumab (n=62) and oxaliplatin / 5-FU without bevacizumab (n=43) had been assessed. There was a significant decrease in the degree of tumor viability in the group treated with bevacizumab compared to the group treated solely chemotherapically (45.3% *vs.* 32.9%). Moreover, they found that the therapeutic response in patients treated with bevacizumab was significantly more pronounced in lesions ≤ 4 cm and was independent of the duration of chemotherapy [41,42].

Another multidisciplinary team from The University of Texas, MD Anderson Cancer Center, led by Yun Shin Chun, analyzed 234 liver metastases of colorectal cancer in 50 patients receiving chemotherapy and bevacizumab as first line therapy. The therapeutic response was interpreted with RECIST and based on the morphological features on DCE-CT (Dynamic Contrast Enhanced-CT): overall attenuation, tumor-liver interface, and peripheral rim of enhacement. A correlation between therapeutic response assessed by these criteria and morphopathological analysis was found. For the validation another group of 87 patients who underwent chemotherapy alone was used, finding a correlation between CT features of morphopathological response and overall survival, but not the same correlation as when RECIST was used [33].

These studies, by the used methods, suggest the superiority of morphopathological criteria in the assessment of therapeutic response. In addition to the size and number of assessed lesions, the imaging tests performed after therapy reveal structural changes of target lesion (deformation of tumor contour, areas of tumor necrosis, mucinous cell-free areas, areas of fibrosis) and peritumoral area (blood supply reduced and stopped with or without reduction in tumor size, areas of fibrosis). The use of such criteria would change the assignment of patients according to response to treatment and decision on resectability conversion with a direct impact on survival and improved quality of life. An area of peritumoral fibrosis of several millimeters could make the difference between a R0 and a R1 resection.

Conclusions

Conversion to resectability rate (CRR) is 7/28 patients (25%) after 9 months.

The absolute disease progression time interval (ADPT) is 3 months for 11 patients, 6 months for 4 patients, and 9 months for 1 patient.

The absolute disease progression rate (ADPR) is the 5/28 patients (17.85%) at 3 months, of 14/28 patients (50%) at 6 months and 18/28 patients (64.28%) at 9 months.

Rigorous surveillance of patients with CRLM according to a well-established scientific protocol with their integration into classes of liver resectability and control at 3 months (after 3 cycles of chemotherapy) represent the first step in onco-surgical therapeutic strategy. An improved rate of conversion to resectability could be achieved through regular assessment of treatment response based on international criteria including besides the number and size of target lesions the post-therapeutic tumor morphological changes.

Response assessment according to RECIST criteria can not confirm the resectability of CRML; according to RECIST, signs of stable disease may be an indication for liver resection in patients with possibly or susceptible resectable metastases.

Using response assessment criteria adapted to the new therapeutic and technological discoveries, will be felt in the way of communication one with another in the multidisciplinary team, and with the patient.

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Conflict of interests

Authors have no conflict of interests to disclose.

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Research Article Open Access

Current Surgical Therapy of Gastroduodenal Ulcer Disease

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Abstract

Introduction: Peptic ulcer is still a very common pathology which exposes the patient to life-threatening complications. This retrospective observational study aims a comparison between current different therapeutic strategies and the advantages and disadvantages in order to improve them.

Material and Method: The study group is composed of 108 patients, 96 hospitalized in Emergency Hospital Bucharest (EHB) and 12 patients hospitalized in Louis-Mourier Hospital, Paris, for the period of 3 years. Were included in the study patients with peptic ulcer and with complications of peptic ulcer treated surgically.

Results: The most common location of peptic ulcer identified in our study was the anterior bulbar duodenum wall. The posterior lessions were penetrating in the pancreas in 78.56% of cases (correlation coefficient=0.034, p=0.002). The surgical treatment strategy adopted in most cases was the suture of the ulcer with or without epiplonoplasty (in 37.5% of cases in EHB and in all cases in Louis-Mourier Hospital), the differences were in the approach technique: most interventions in EHB were performed by laparotomy. The surgical management of perforation was in most cases gastrectomy followed by bulbantrectomy. The operation of gastrectomy was done at a rate of 65.52% by laparotomy (p=0.001). Regarding the reconstruction of digestive tract, most anastomoses were performed manually. They are mainly gastro-duodeno anastomosis Pean (37%) because it provides a physiological continuity.

Conclusions: Therapeutic management adopted in the two clinics were largely similar, mention the status of population-related differences, socio-economic status and the dinamics of risk factors (NSAID therapy, the incidence of HP, food etc..).

Keywords: Peptic ulcer; Surgical treatment; Gastrectomy; Laparoscopy

Introducere

Ulcerul gastro-duodenal reprezintă încă o patologie destul de frecventă ce expune pacientul la diverse complicații cu risc vital. Indicațiile chirurgicale în sfera gastro-duodenală sunt reprezentate la ora actuală de cancerul gastric și ulcerul gastro-duodenal. Riscul de a avea ulcer în cursul vieții sunt considerabile având în vedere că unul din factorii de risc este stresul, iar acesta are un nivel crescut în ziua de azi. Costurile sunt și ele semnificative și se referă la spitalizare, medicație, scăderea producției și invaliditate. Astăzi, chirurgia este indicată în situația apariției complicațiilor sau în cazul eșecului tratamentului medicamentos și endoscopic. Aceste tratamente complementare au redus considerabil numărul intervențiilor chirurgicale pentru această patologie, dar nu au putut elimina complicații precum perforația, penetrația sau stenoza. [1-3]

Plecând de la aceste afirmații am încercat să determinăm tipul intervențiilor folosite pentru diversele complicații, avantajele și dezavantajele acestora și modul de abord chirurgical. Am adunat informații din două clinici diferite ca țară de origine (Romania și respectiv, Franța), putând astfel compara abordările acestora. Managementul chirurgical diferit din cele două clinici trebuie însă privit integrativ în ceea ce privește diferențele populaționale de status socio-economic, factorii de risc, speranța de viață și media de vârstă în cadrul celor două medii.

Importanța temei abordate privind în special complicațiile ulcerului gastro-duodenal va fi permanent în atenția chirurgilor până atunci când se va eradica complet *Helicobacter pylori* (HP), se vor elimina antiinflamatoarele non-steroidiene (AINS) și se va modifica mentalitatea adresabilității pacientului la medic.

Material și metodă

Lotul studiat a cuprins un număr de 108 pacienți, 96 internați în cadrul Clinicii de Chirurgie Generală a Spitalului Clinic de Urgență București (SCUB) în perioada ianuarie 2009 – martie 2012 și 12 pacienți internați în cadrul Clinicii de Chirurgie Generală și Digestivă a Spitalului Louis-Mourier - Hôpital Universitaire Paris Nord Val de Seine, Paris, Franța în aceeași perioadă de 3 ani. Au fost introduși în studiu pacienții cu patologie ulceroasă gastro-duodenală la care tratamentul acestei afecțiuni a fost unul chirurgical prin intervenții laparoscopice sau prin laparotomie și pacienți tratați chirurgical în urgență pentru complicații survenite în urma bolii ulceroase. Baza de date a fost analizată statistic (analiză univariată) iar valorile medii au fost prezentate ca medie ± derivația standard.

Rezultate

Analiza descriptivă a întregului lot de 108 pacienți relevă o

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distribuție relativ egală în ultimii doi ani cu o ușoară tendință de scădere a intervențiilor chirurgicale pentru aceasta patologie (Tabel I)

În ceea ce privește distribuția pe sexe, un procent de 70,83% pacienți de sex masculin au fost ânregistrati în cadrul Clinicii SCUB și un procent de 75% în cazul pacienților din cadrul Clinicii spitalului Louis-Mourier. Incidența maximă s-a înregistrat la grupa de vârstă 50-59 de ani (Clinica SCUB), un număr asemănător de cazuri au fost și în decadele 40-49 de ani si 60-69 de ani. Aceeași distribuție regăsindu-se și în alte studii din literatură realizate în alte clinici [4,5].

În cadrul Clinicii Spitalului Louis-Mourier, distribuția se menține asemănătoare, numărul maxim de cazuri fiind tot în intervalul de vârstă de 50-59 de ani, însă grupele inferioare acesteia au înregistrat valori mai mari comparativ cu grupele superioare. Se observă astfel o ușoară diminuare a vârstei la care se face intervenția în această clinică. Trebuie totuși ținut cont și de parametrii socio-economici și culturali, dar mai cu seamă de media de vârstă, speranța de viață în populația respectivă și dinamica factorilor de risc (tratamentul AINS, incidența HP, alimentația etc.).

Trebuie menționate vârstele extreme, astfel în cadrul Clinicii SCUB vârsta minimă a fost de 23 de ani, iar cea maximă de 84 de ani, cu o medie de vârstă de 52,07 ± 15,342 ani. În cadrul Clinicii Spitalului Louis-Mourier, vârsta minimă a fost de 29 de ani, iar cea maximă de 82 de ani, cu o medie de 46,5 ± 14,805 ani.

În Clinica SCUB, majoritatea pacienților au prezentat perforația ulcerului cu peritonita adiacentă acestei perforații. Totuși 6,25% (n=6) din cazuri s-au prezentat foarte rapid și astfel nu a avut timp pentru a se instala peritonita. Un număr aproximativ egal de cazuri (n=21) au prezentat un ulcer hemoragic, stenozant la nivel piloric sau pentrant în organele adiacente localizării acestuia. În cadrul clinicii Louis-Mourier toate cazurile au prezentat perforația și/sau peritonită ca principală complicație.

În ceea ce privește dimensiunile leziunilor ulceroase am împărțit totalul leziunilor în 4 clase [5,6] astfel: ulcere de dimensiuni mici (până în 5 mm), ulcere de dimensiuni medii (între 5 mm și 10 mm), ulcere de dimensiuni mari (între 10 mm și 30 de mm) și ulcere gigant (peste 30 de mm). În urma repartiției cazurilor pe cele patru grupe, în cadrul Clinicii SCUB se observă o majoritate de cazuri în grupa de ulcere medii (51,04% din totalul cazurilor, acest procent reprezentând 49 de cazuri), în grupa de ulcere mici, de sub 5 mm se întâlnesc 15,62% din cazuri (reprezentând 15 cazuri), un procent asemănător se întâlnește și în cazul ulcerelor mari (17,70% din totalul cazurilor, adică 17 cazuri), iar în clasa ulcerelor gigant se înregistrează 12,5 % din cazuri (reprezentând 12 cazuri). Trebuie să menționăm faptul că 3 leziuni ulceroase nu au putut fii măsurate și astfel au fost excluse din cele 4 clase de ulcere.

În vederea analizei statistice în cadrul problemei studiate am împarțit leziunile în cele două mari categorii (ulcer gastric - UG, ulcer duodenal – UD) și am regăsit un procent de 26,04% de UG și 73,96% de UD, date asemănătoare fiind citate și în literatura de specialitate [5-8] (în special pentru sexul masculin, care și în cazul nostru este majoritar însă între cele două variabile nu există corelație semnificativă statistic $p > 0,05$).

Localizarea anterioară, cea mai întâlnită, a ulcerelor păstrează un procentaj asemănător și în funcție de sex, astfel din cele 96 de cazuri întâlnite în Clinica SCUB, localizarea bulbară duodenală anterioară a ulcerelor a fost prezentă în 58,82% dintre pacienții de sex masculin și în 60,71% dintre pacienții de sex feminin.

Nu am găsit nicio corelație între localizarea ulcerului și sexul sau grupele de vârstă ale pacienților, în cele doua clinici, leziunile fiind aproximativ egal distribuite ($p > 0,05$).

Cel mai important aspect în chirurgia ulcerului gastro-duodenal este reprezentat de complicația acestuia, astfel dictând ulterior managementul chirurgical.

Strategiile terapeutice adoptate în cadrul Clinicii SCUB în majoritatea intervențiilor a fost sutura simpla a orificiului ulceros (în proporție de 37,5%), această sutura fiind însoțită în proportie de 77,77% de epiploonoplastie ($p < 0,05$). Nu la o diferență foarte mare se înregistrează operația de gastrectomie 2/3, în proporție de 30,2%, știut fiind faptul că intervențiile cu rezecție gastrică sunt recomandate în majoritatea cazurilor de ulcer clasa Johnson I, IV [2,9-11]. Celelalte trei strategii operatorii: ulcero-rezecția cu sau fără piloroplastie, hemostaza in situ și bulb-antrectomia au fost realizate în 17,07% (n=17), 11,45% (n=11) și respectiv 6,25% (n=6) din cazuri. Sutura ulcerului a fost realizată în special pentru ulcerele duodenale bulbare anterioare, procentul acestora fiind semnificativ statistic (p=0,007).

Această împărțire pe tipul de intervenții chirurgicale alese nu aduce informații foarte prețioase decât dacă le raportăm la tipul complicației ulceroase.

Astfel, sutura ulcerului a fost realizată în special pentru ulcerele perforate (57,57%) (Figura 1), cu localizare duodenală bulbară anterioară, procentul acestora fiind semnificativ statistic (p=0,007). Această decizie a fost luată datorită dimensiuniilor și localizării ulcerelor, pentru a minimiza timpul operator și rata complicațiilor chirurgicale postoperatorii. Pentru ulcerele penetrante (Figura 2) a fost preferata fie sutura ulcerului (50%), fie gastrectomia (bulbantrectomia) (20%). Cazurile de ulcerorezecție cu piloroplastie fiind doar 15%. În cazul ulcerelor hemoragice intervenția preferata a fost gastrectomia (Figura 3). Un procent semnificativ de pacienți (38%) au fost tratați prin hemostaza in situ, pentru a reduce timpul operator și complicațiile postoperatorii, argumente citate și în literatură [12]. Rezecția gastrică, a fost preferată și pentru ulcerele stenozante (Figura 4).

În cadrul Clinicii Louis Mourier intervențiile au prezentat ulcer perforat și s-au soluționat în principal prin sutura ulcerului cu sau fără epiploonoplastie.

Nu a existat, în niciuna dintre clinici, nicio corelație între tipul intervenției și grupele de vârstă sau sex, cu excepția epiploonoplastiei care a fost aparent preferată pentru bărbați (p=0.04; 95%CI 0.010-0.406).

Refacerea continuității digestive după rezecția gastrică s-a realizat prin anastomoză Pean (gastro-duodenală) în 37% din cazuri; în cazul rezecțiilor gastrice, în care nu s-a putu realiza anastomoza gastro-duodenală termino-terminală din motive tehnice/anatomice (sutură în tensiune) s-a realizat fie anastomoza gastro-jejunală pe ansă în "Y" à la Roux (22%), fie anastomoză Hoffmeister-Finsterer (16%), fie anastomoză gastro-duodenală latero-terminală (16%). Au fost realizate și câteva anastomoze tip Reichel-Polya (6%) și gastro-jejuno anastomoză pe ansă în omega (3%) (Figura 5). Rezecția gastrică a fost efectuată în proporție de 65,52% prin laparotomie, iar majoritatea anastomozelor au fost realizate manual (84.37%).

Discuții

Localizarea cea mai frecventă a ulcerului gastro-duodenal a fost cea duodenală bulbară anterioară (în 59.35% din cazurile Clinicii SCUB și în 100% din cazurile Clinicii Spitalului Louis-Mourier). De

Tabel I: Distribuția anuală a pacienților în cele două servicii de chirurgie.

Anul	SCUB (n)	SCUB (%)	Spital Louis-Mourier (n)	Spital Louis-Mourier (%)	n
2009	34	35,42	3	25,00	37
2010	36	37,50	4	33,33	40
2011	23	23,96	4	33,33	27
2012	3	3,13	1	8,33	4
n (total)	96	100	12	100	108

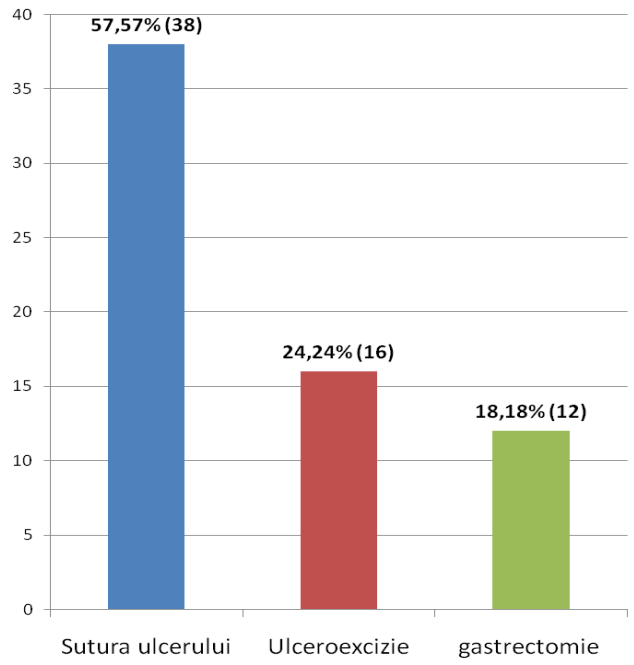

Figura 1: Managementul chirurgical în cazul ulcerului complicat cu perforație.

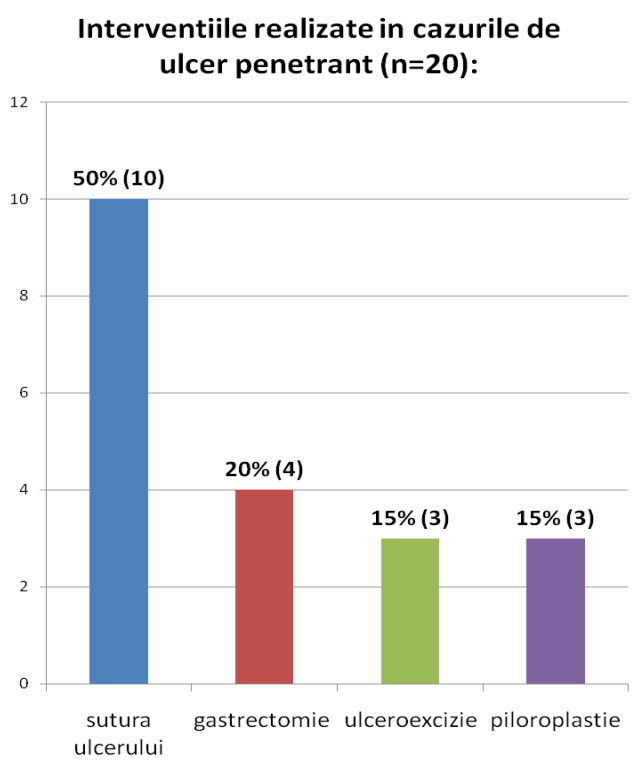

Figura 2: Managementul chirurgical în cazul ulcerului penetrant.

asemenea, strategia terapeutică chirurgicală adoptată în majoritatea cazurilor, în cele doua clinici, a fost cea de sutură a ulcerului cu sau fără epiploonoplastie (în 37.5% din cazurile Clinicii SCUB și în toate cazurile Clinicii Louis-Mourier), diferențele fiind la modul de realizare al acesteia, Clinica SCUB realizând majoritatea intervențiilor prin laparotomie, ținând cont de cazurile mai numeroase de contraindicație pentru laparoscopie, în timp ce Clinica Spitalului Louis-Mourier, neavând atât de multe cazuri cu contraindicație pentru laparoscopie a folosit această tehnică pentru 75% din cazurile operate. Frecvența abordării minim invazive trebuie privită în contextul diferentelor socio-economice, al factorilor de risc (HP, AINS, alimentatie etc.) și al speranței de viață și mediei de vârstă a populației [11].

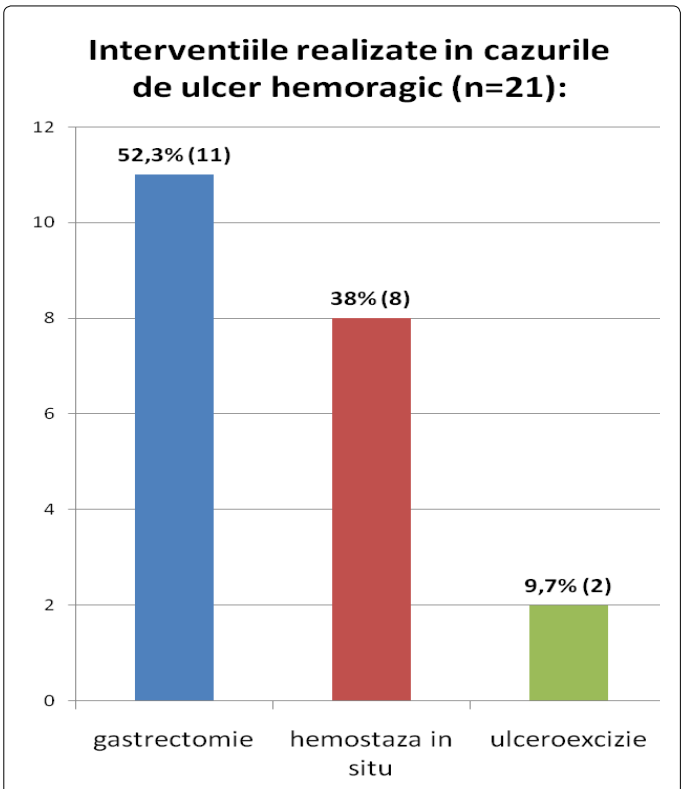

Figura 3: Managementul chirurgical in cazul ulcerului complicat cu hemoragie.

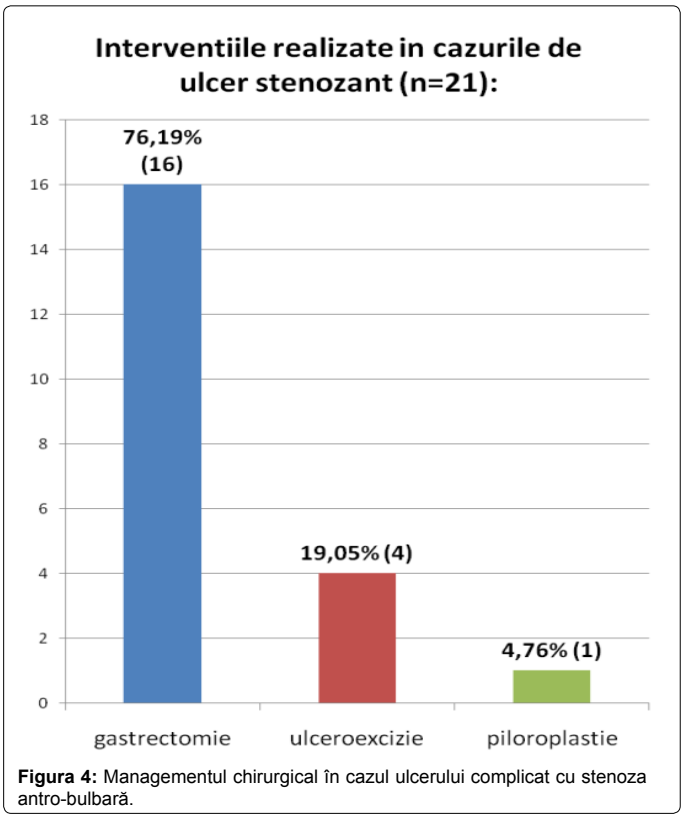

Figura 4: Managementul chirurgical în cazul ulcerului complicat cu stenoza antro-bulbară.

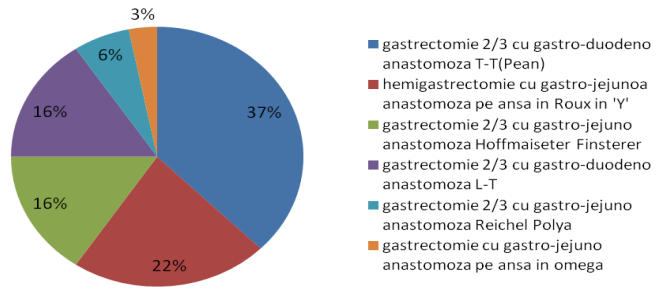

Figura 5: Modalitîțile de refacere a continuității digestive post-gastrectomie.

Diferența dintre numărul operațiilor realizate laparoscopic și prin laparotomie dintre cele doua clinici credem că se datorează, pe lângă numărului mai mare de cazuri cu contraindicație pentru laparoscopie existent în Clinica SCUB, și statutului economico-politic al statului nostru, diferenței de buget al spitalelor și adresabilitatea mai mare către medic, Clinica Spitalului Louis-Mourier având buget superior, tehnică de ultimă generație, și planuri de screening și tratament bine implementate. De asemenea, vârsta cazurilor cu adresabilitatea maximă către medic a fost mai mică. Aceste rezultate sunt în concordanță cu cele obținute în studii similare atât în România cât și în alte țări [4,6,13,14].

În ceea ce privește ulcerele hemoragice și stenozante, a fost indicată gastrectomia, procedeu rezecțional, astfel eliminându-se complet sursa hemoragică sau stenozantă, eliminând posibilitatea de recidivă și se poate evalua și histopatologic piesa de rezecție în vederea eliminării diagnosticului de malignitate. Pericolul potențial de malignizare, în acest caz reprezentând un criteriu în favoarea procedeului rezecțional.

Opțiunea operației de urgență trebuie efectuata în baza evaluării gradului riscului operator [15], stabilității hemodinamice, sediului și dimensiunilor ulcerului, activității hemoragiei ulceroase sau a riscului de perforație / penetrare.

Concluzii

În efectuarea intervenției chirurgicale la bolnavii cu ulcer al peretelui anterior al duodenului, este de preferat operația conservatoare: sutura ulcerului cu sau fără epiploonoplastie. În cazul ulcerului peretelui duodenal posterior hemoragic sau stenozant, metoda de elecție este rezecția gastrică. În ceea ce privește refacerea continuității digestive, majoritatea anastomozelor au fost realizate manual, anastomoza gastro-duodenală tip Pean fiind preferată. Pentru cazurile dificile în care nu a fost posibilă anastomoza Pean se poate realiza o anastomoză gastro-jejunală de tip Roux sau Hoffmeister-Finsterer.

Conflict de interese

Autorii nu declară nici un conflict de interese.

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Journal of Surgery
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Research Article Open Access

Conventional Minimally Invasive Parathyroidectomy for Single Parathyroid Adenoma

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Abstract

Background: Minimally invasive parathyroidectomy is actually the gold standard in the treatment of primary hyperparathyroidism (PHPT) due to parathyroid adenoma (PA).

Material and Methods: A clinical retrospective study was performed on a series of 40 cases operated for pHPT by single PA from January 2013 to March 2015, in the surgical department of the "St. Spiridon" Hospital of Iasi, a refferal center for endocrine surgery. Biochemical markers achieved the diagnosis of PHPT and PA was localized using cervical US and MIBI scintigraphy. Conventional minimally invasive parathyroidectomy (C-MIP) was performed in all cases where PA was accurately localised by preoperative imaging, whereas conventional cervical exploration was necessary in cases with concomitant thyroid pathology.

Results: Preoperative localisation findings were concordant with the intraoperative findings, except for one case when conversion to bilateral exploration was deemed and the PA was identified on the other side. In 8 cases, additional thyroid pathology – uni/multinodular goiter and a papillary microcarcinoma imposed a conventional PT adenomectomy and concomitant lobectomy/total thyroidectomy. The values of calcemia and PTH decreased significantly postoperatively and reached normal range in all cases. With the exception of a transient reccurrent nerve paresis (in a patient with total thyroidectomy), no postoperative morbidity and mortality was encountered.

Conclusion: Conventional mini-incision parathyroidectomy (C-MIP) has an excellent cure rate and minimal morbidity, with a reduced hospital stay and cost compared with the conventional extensive approach.

Keywords: Primary hyperparathyroidism; Minimally invasive parathyroidectomy; Adenoma

Introduction

Primary hyperparathyroidism (pHPT) is defined as symptomatic hypercalcaemia due to excessive parathyroid hormone (PTH) secretion in the absence of secondary or tertiary causes. Although underdiagnosed in the past, the incidence of PHPT rose significantly due to routine determination of serum calcium and accessible PTH measurement combined with routine neck US and longer life span expectancy. Parathyroidectomy is the definitive treatment for primary hyperparathyroidism (pHPT) due to PA [1]. Although classical surgical approach has been cervicotomy with bilateral neck exploration and a four-gland evaluation approach, from the late 90', minimally invasive techniques developed. Directed by accurate preoperative localisation, unilateral exploration and evaluation limited to the site of suspected lesion were succesfully performed by video-assisted parathyroidectomy (Micolli, 1997), endoscopic parathyroidectomy (Henry 1999) and conventional (open) mini-incision parathyroidectomy (C-MIP) [2,3]. The aim of the study was to report the initial experience and outcome of C-MIP in the treatment of pHPT due to PA in the IIIrd Surgical Unit.

Material and Methods

A clinical retrospective study was performed on a series of 40 cases operated for pHPT by single PA during January 2013 - March 2015, in the surgical department of the "St. Spiridon" Hospital of Iasi, a referral center for endocrine surgery. Among these, C-MIP was performed in 31 cases whereas bilateral cervical exploration and PA was performed in 9 cases.

Preoperatively, a team composed of endocrinologist, nuclear medicine specialist, surgeon, anesthetist and pathologist investigated the patients. Biochemical markers achieved the diagnosis of PHPT and PA was localized using cervical US and MIBI scintigraphy. C-MIP was performed in all cases where preoperative imaging accurately localized PA, whereas conventional cervical exploration was necessary in cases with concomitant thyroid pathology. Under general or local anesthesia, a 2-2.5 cm transverse incision was sited over the presumed location of the lesion and the PAwas identified and removed by lateral ("back-door") approach, with visualisation of the reccurrent laringeal nerve (RLN). Intra- and postoperative levels of PTH were recorded (after removal of PA and frozen section pathology exam confirmation). No drainage was used, the skin wound was closed with an absorbable intradermic suture and the patients were discharged on postoperative day two.

Surgical procedure was considered successful when intraoperative frozen section confirmed the removal of PT tissue, quick PTH decreased more than 50% of the preoperative value and when normalization of

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PTH and calcium levels occurred postoperatively. PTH was measured by chemiluminescence with Siemens commercial kits compatible with the automatic analyzer Immulite 2000 (Siemens).

A permission of the hospital and "Gr.T. Popa" University of Medicine Ethics Comission was granted for the study.

Results

The patient's demographic data, pre- and postoperative endocrine profile and adenoma characteristics are featured in Table I. The majority of the patients were female (85%) in the age decade 40-50. C-MIP was successfully performed in 31 cases, with a medium operative time of 42 minutes, including the frozen section waiting interval of approximately 20 minutes. Preoperative localization findings were concordant with the intraoperative findings, except for one case when conversion to bilateral exploration was deemed and the PA was identified on the other side. In 8 cases, additional thyroid pathology–uni/multinodular goiter and a papillary micro carcinoma imposed a conventional PT adenomectomy and concomitant lobectomy/total thyroidectomy. The values of calcemia and PTH decreased significantly postoperatively within normal range in all cases, as shown in Figure 1 and 2. With the exception of a transient RLN paresis (in a patient with total thyroidectomy), no postoperative morbidity and mortality was encountered.

Discussions

PHPT is a quite common endocrine disorder, which often causes no symptoms, being the most important cause of hypercalcemia. The pathophysiologic basis of PHPT is an excessive secretion of PTH from one ore more parathyroid glands which causes raised calcium levels in the blood.

PHPT is diagnosed much more often than before, since determination of calcium in serum became a routine and since the possibility to determine parathyroid hormone values became largely accessible [4]. Before offering parathyroid surgery, the surgeon must carefully review and confirm the preoperative diagnosis to avoid unnecessary surgery. Errors in diagnosis are a major cause of failed initial exploration. The benefits of surgery are obvious for patients with symptomatic hypercalcemia [5].

The combination of hypercalcaemia and elevated serum PTH concentration is decisive in achieving the diagnosis of PHPT. Further on, imagistic studies, consisting of the standard association between cervical US and MIBI scan, may accurately locate the PA and endorse a successful surgical removal, preferably minimally invasive [6]. A successful parathyroidectomy restores serum calcium levels to the normal range; this resolves metabolic complications of hypercalcemia and may also improve symptoms and quality of life. Successful parathyroidectomy also cuts back the accelerated bone loss, reduces the risk of renal stone formation and has an important result in reducing of nonspecific symptoms associated with hyperparathyroidism [7].

The benefits of minimally invasive PT adenomectomy are obvious - shorter operating time and hospital stay, a smaller and cosmetically acceptable wound and overall greater patient satisfaction with similar success rate as the conventional method [8,9]. Precise pre-operative localisation has allowed a rapid development of the video-assisted, endoscopic and radio-guided techniques, but C-MIP remains the most widely used minimally invasive method [10,11]. Another important advantage of C-MIP is the option of local infiltration or regional block anaesthesia in selected cases, thus avoiding the risk of general anaesthesia and intubation, shorter recovery time following the operation, lower post-operative pain and lower incidence of nausea and vomiting [12]. Local anesthesia by infiltration was used in only 4 cases in our series, mainly due to the reticence of the patients for the procedure.

Table I: Patients and Adenoma characteristics.

N (patients)	40	
Age (years old, mean ± SD)	45 ± 5	
Men / Women (N, %)	6 (15%) / 34 (85%)	
Perioperative endocrine profile	**Preoperative**	**Postoperative**
Calcium (mg/dL, mean ± SD)	11.62 ± 1,337	9.37 ± 1.315
Parathyroid hormone (ng/L, mean ± SD)		
Adenoma characteristics		
Weight (g, mean ± SD)	0.095 ± 0.037	
Estimated volume (mm^3)	2,197 ± 0,0379	

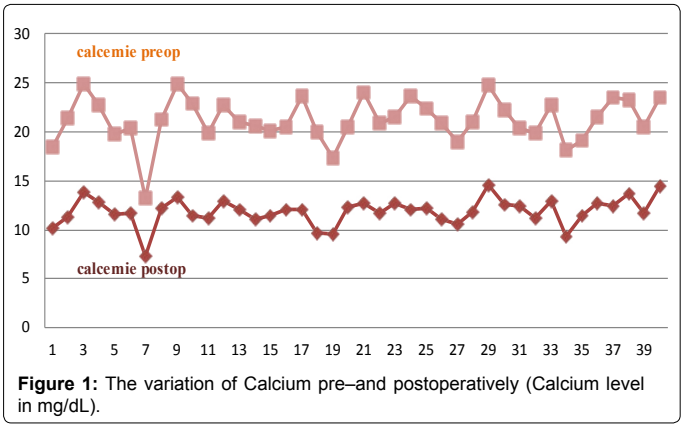

Figure 1: The variation of Calcium pre–and postoperatively (Calcium level in mg/dL).

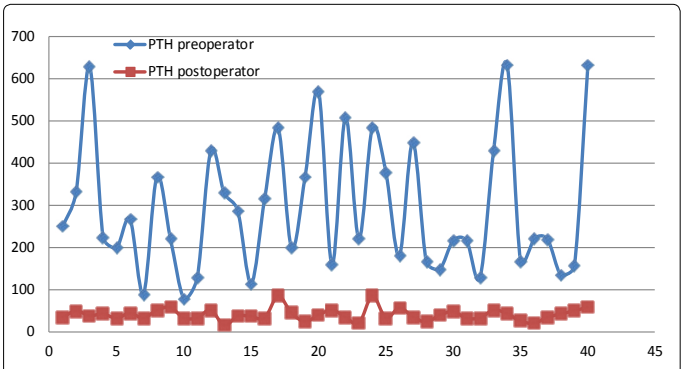

Figure 2: The variation of PTH pre–and postoperatively (PTH level in ng/L).

Conclusion

Conventional mini-incision parathyroidectomy (C-MIP) has an excellent cure rate and minimal morbidity, with a reduced hospital stay and cost compared with the conventional extensive approach.

Conflict of interests

Authors have no conflict of interests to disclose.

Acknowledgements

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Journal of Surgery
[Jurnalul de Chirurgie]

Case Report Open Access

Dyke-Davidoff-Masson Syndrome: A Cause of Recurrent Seizures

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Abstract

Objective: Dyke-Davidoff-Masson Syndrome (DDMS) is one of the rare causes of recurrent seizures and can be missed in adults. It is associated with contralateral hemiplegia, mental retardation and facial asymmetry. Confirmed diagnosis can be made with characteristic radiological picture. Hemi-spherectomy is the treatment of choice.

Case: DDMS is usually diagnosed in childhood. Here a rare case of refractory epilepsy is being reported in a 23 years old pregnant woman which was diagnosed as DDMS on radiological findings of cerebral atrophy, ventricle enlargement, dilatation of sulci and osseous hypertrophy of calvarium with increased width of diploic space.

Conclusion: A proper history, thorough clinical examination and characteristic radiological findings provide the correct diagnosis of DDMS. CT/MRI must be performed in patients presenting with recurrent seizures.

Keywords: DDMS; Cerebral hemiatrophy; Recurrent seizures; Refractory epilepsy

Introduction

The most common cause of recurrent seizures is attributed to epilepsy. Though refractory epilepsy is common in neurology practice, Dyke-Davidoff Masson syndrome (DDMS) is one of the rare syndromes associated with it. DDMS includes mainly neurologic symptoms, such as seizures, facial asymmetry, contralateral hemiplegia, and mental retardation. Radiologic study reveals cerebral hemiatrophy, ventricle enlargement, shift to the affected side, dilation of sulci, and compensatory skull changes [1].

DDMS is usually diagnosed in childhood but rare cases have been reported in teenagers and adults [2-4]. We are reporting an interesting case of refractory epilepsy in a 23 years old pregnant woman who was later diagnosed as a case of Dyke-Davidoff Masson syndrome (DDMS).

Case Report

A 23-years-old primigravida, married for two years, presented to our department with seven months pregnancy and recurrent episodes of seizures. On examination, the patient was mentally subnormal but conscious to her surroundings. Her blood pressure was normal and urinary proteins were negative. She had facial asymmetry and right sided hypertonic exaggerated reflexes. Per Abdomen examination revealed 28 weeks size relaxed uterus with cephalic presentation and regular fetal heart rate. There was a history of fits earlier for which she had taken irregular treatment. A provisional diagnosis of seizure disorder (epilepsy) was made. Patient was put on injectable phenytoin which is used as first line of drug for and she responded. After 2 days, she again had seizures and injectable sodium valproate was added. After a seizure free period of one week, patient was discharged on oral medication of phenytoin and sodium valproate. She reported again with seizures after 3 days and on detailed evaluation, it was found that she was not compliant. Injectable sodium valproate and phenytoin were restarted and the patient responded. Her routine haematological and biochemical investigations were within normal limits. Sonographic assessment of foetus was normal. After one week, she developed mild pre-eclampsia with blood pressure of 150/96 mm/Hg and 1+ urinary protein. Due to prematurity, conservative management was continued along with 6 hourly BP charting and foetal monitoring.

At 32 weeks of gestation, the patient complained of loss of fetal movements. Her blood pressure was found to be 160/110 mm Hg with 2+ urinary proteins. Per abdomen examination revealed 34 week size tender and tense uterus with absent foetal heart sounds. Ultrasound examination confirmed intra-uterine death. Diagnosis of severe pre-eclampsia with abruption was made. Bishop's score was 5/13. Artificial rupture of membranes obtained haemorrhagic liquor. Labour was augmented with oxytocin. Patient did not deliver even after ten hours of augmentation and cervical dilatation did not improve beyond 5cm. Caesarean section was performed in view of abruptio placentae with non-progress of labour and a dead female child weighing 2 Kg was delivered. Intra-operative period was uneventful. Post-operatively, patient had seizures which were not controlled with injectable phenytoin and sodium valproate. She became disoriented and irritable. On enquiring repeatedly, patient's mother revealed the fact that she was a known case of seizure disorder since 10 years of age when she had sudden onset of generalised tonic clonic seizures and right sided hemiplegia. She recovered with medication but right sided weakness and facial asymmetry persisted. Since childhood, patient was taking phenytoin irregularly.

CT scan of head showed left cerebral atrophy, ventricle enlargement, dilatation of sulci and osseous hypertrophy of calvarium with increased width of diploic space on left side (Figure 1). A diagnosis of Dyke-Davidoff-Masson syndrome was made. Neurologist opinion was sought who started injection phenobarbitone. Seizures were controlled but the Glasgow coma scale remained 6/15 may be due to the added complication of pregnancy induced hypertension. The patient developed disseminated intravascular coagulation with multi-organ dysfunction, probably as a complication of severe pre-eclampsia and expired on 5th post-operative day.

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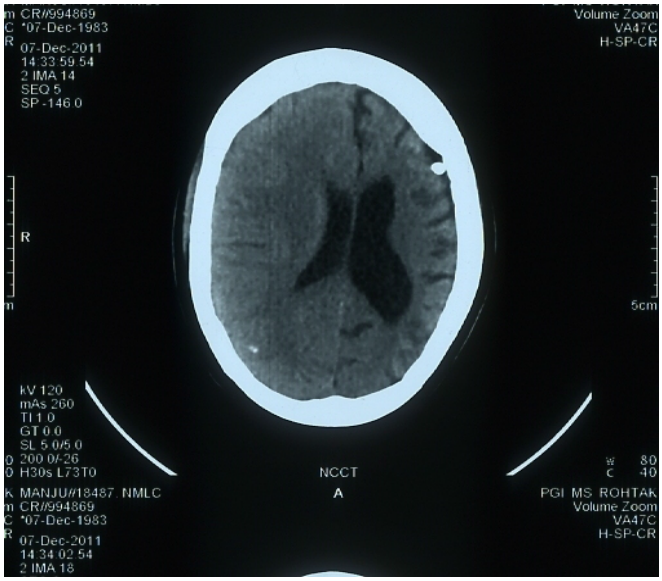

Figure 1: NCCT Picture.

Discussion

For planning the management of recurrent seizures, first step is to identify the cause for seizures. Neuroimaging has proven to be the main tool in investigation of seizure disorder.

Dyke-Davidoff-Masson Syndrome (DDMS) is one amongst the syndromes associated with refractory epilepsy. Dyke-Davidoff and Masson described the plain skull radiographical features of Dyke-Davidoff-Masson Syndrome (DDMS) in 1933. This was described in a series of 9 patients with hemiparesis, seizures, facial asymmetry and mental retardation. The radiographical features of the skull were asymmetry, ipsilateral osseous hypertrophy of the calvarium and hyper-pneumatization of the sinuses [5]. The disease is classified into infantile (congenital) and acquired type. In the infantile type, the various causes propounded are neonatal or gestational vascular occlusion involving the middle cerebral vascular territory, unilateral cerebral arterial circulation anomalies, coarctation of the mid-aortic arch, mesencephalon hypoplasia and wallerian degeneration. These patients become symptomatic in perinatal period or infancy. The acquired type, results from trauma, infection, ischaemia and haemorrhage. The age of presentation depends on time of insult and the characteristic changes may be seen only in adolescence [6].

The mechanism of cerebral atrophy is still unclear, but it is hypothesized that ischemic episodes from a variety of different causes reduce the production of brain derived neurotrophic factors, which in turn lead to cerebral atrophy [7]. When the brain fails to grow properly, the other structures tend to direct their growth inward, thus accounting for the enlargement of the frontal sinus, the increased width of diploic space and the elevations of the greater wing of sphenoid and the petrous ridge on the affected side [8]. Both the sexes and either of the hemispheres may be affected but male gender and left hemisphere involvement are more frequent. Age of presentation depends on time of neurologic insult and characteristic changes may be seen only in adolescence. The clinical findings may be of variable degree depending on the extent of the brain injury. Varying degrees of atrophy of one half of body, sensory loss, speech and language disorder, mental retardation or learning disability and psychiatric manifestations like schizophrenia may also be present [9].

Narain et al described the case of DDMS in an 18 month-old girl who presented with right sided focal seizures, hemiparesis of same side and delayed milestones. The findings of dilated cortical sulci and widening of ipsilateral diploi reflecting a late onset of brain insult probably of vascular origin involving left middle cerebral artery [9].

Lee et al. described a case of a 17 month-old male child who presented characteristics of DDMS with left focal clonic or tonic-clonic seizures accompanied by left hemiparesis and developmental delay. Brain MRIs demonstrated progressive atrophy of the right cerebral hemisphere with dilatation of the lateral ventricle, expansion of the ipsilateral frontal sinus with calvarial thickening, and elevation of the petrous pyramid and orbital roof. Brain Single-photon emission computed tomography (SPECT) showed a decreased volume of the right hemisphere with reduced blood flow [10].

Amann et al. report the first case of left cerebral hemiatrophy and a late onset of treatment-resistant schizoaffective disorder after a stressful life event. Magnetic resonance imaging (MRI) revealed left cerebral hemiatrophy with loss of white matter and gliosis in frontal, temporal, and in posterior areas. Pyramidal degeneration and a left mesencephalic hemiatrophy with a slimming of the corpus callosum were also noted. A slight atrophy at the right hemisphere and cerebellum was observed [2].

The condition needs to be differentiated from Basal ganglia germinoma, Sturge Weber syndrome, Linear nevus syndrome, Fishman syndrome, Silver-Russell syndrome and Rasmussen encephalitis [11,12].

The manifestations of DDMS may be as subtle as to be overlooked on plain radiographs; however, CT is the diagnostic modality of choice [3]. *Lee and Amann* had diagnosed DDMS on MRI [2,10].

The treatment of DDMS with multiple anti-epileptics is the best option. If the seizures are refractory, hemi-spherectomy is the best treatment option [4].

On searching the literature, no case of DDMS in pregnancy could be found and our case appears to be the first one. Generalized seizures during pregnancy can lead to increased maternal trauma which can result in intra-cranial haemorrhage in foetus and if maternal abdomen is involved, a theoretical risk of abruption exists, possibly leading to foetal hypoxia or death. Furthermore, the risk of maternal aspiration can cause maternal hypoxia, which can also lead to fetal hypoxia. Repeated convulsions during pregnancy can significantly increase the maternal and foetal morbidity and mortality. In the present case, the foetus died in utero but the likely cause of intrauterine death appears to be abruptio placentae due to severe pre-eclampsia. Apart from seizures the precise effect of DDMS on foetus is not documented in literature as this is the first reported case of DDMS in pregnancy.

In our case, exact diagnosis could not be made in ante-natal period due to the incomplete history given by patient and attendants as the tendency in developing countries is to hide the facts about chronic disease. CT scan was delayed due to limitation of radiation exposure in pregnancy though the period of teratogenesis was over but still there does exist a risk of carcinogenesis. At the same time the patient responded to anticonvulsants initially and the facility of MRI was not available at that time in the hospital. It could have been diagnosed and managed earlier but due to low socioeconomic status and unawareness, the disease could not be diagnosed till adulthood. No definitive management (hemi-spherectomy) could be done in post-operative period as the general condition of the patient was poor.

Conclusion

DDMS can be diagnosed by the assessment of patient by complete clinical history and examination along with radiological features on CT/MRI. In patients of recurrent seizures, CT/MRI should be considered as early as possible.

Conflict of interests

Authors have no conflict of interests to disclose.

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Journal of Surgery
[Jurnalul de Chirurgie]

Case Report Open Access

Synchronous Perforation of Transverse and Sigmoid Colon due to Ulcerative Colitis: A Rare Case Report

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Abstract

Acute severe ulcerative colitis is a potentially life-threatening condition that requires a pro-active approach with either effective medical treatment or timely colectomy. The possibility of free perforation in ulcerative colitis must be considered in fulminating cases. This report describes a 39 -year- old female with known ulcerative colitis on maintenance medical therapy. She was admitted for peritonitis, and intraoperative findings revealed a synchronous colonic perforation. After multidisciplinary discussion she was managed with total colectomy and end ileostomy.

Keywords: Colonic perforation; Ulcerative colitis; End ileostomy

Introduction

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD) and Ulcerative Colitis (UC). These autoimmune conditions involve mucosal inflammation of the entire gastrointestinal tract in CD and the colon and rectum in UC [1]. While primary management of IBD is medical, surgical indications are generally reserved for toxic colitis, perforation, bleeding, strictures, neoplasms, and failure of medical management.

Perforation of the colon is the most dangerous local complication of the disease. The colon does not form adhesions in ulcerative colitis and the consequence is that, if perforation does occur, it usually results in a generalized faecal peritonitis which is extremely dangerous. Although there are sometimes the classical signs of a perforation, the condition may produce few local signs and the only indication that some disaster has occurred is a marked deterioration in the general condition of the patient.

Toxic dilatation of the colon is one of these rare complications and it is well recognized that if it is not effectively treated it may go on to perforation [2]. Perforation in association with UC is even less common than toxic dilatation and although the two conditions may be associated, perforation in UC may occur without dilatation [3]. Here, we report a 39 -year- old female with known ulcerative colitis on maintenance medical therapy. Workup revealed a synchronous colonic perforation. After multidisciplinary discussion she was managed with total colectomy and end ileostomy.

Case Report

A 39-year-old woman was admitted to the Emergency Department with complaints of abdominal pain, nausea and vomiting for 2 days. The pain was constant and located primarily in the periumblical area, and then became generalized. She had been under medical treatment for ulcerative colitis (UC) for 15 years, but had continued to have symptoms of anaemia and bloody diarrhea. Bouts of diarrhea were occurring up to 10 times a day with blood apparent in the feces. She was diagnosed with UC via symptoms and colonoscopic evidence of disease. Her medical history included diabetes mellitus and epilepsy.

On physical examination, her blood pressure was 110/60 mmHg, pulse rate 104 beats/minute, body temperature 38.4°. Lung and heart sounds were normal but heart rhythm was tachycardia. The abdomen was distended and tenderness was noted to direct and rebound palpation with guarding in all quadrants.

The laboratory findings revealed; sodium of 142 mmol/L; potassium of 3.1 mmol/L, white blood cell count (WBC) 18.7×103/µL, Hemoglobin (Hb) 9.2 g/dL and Platelets (Plt) 372×103/µL. In liver chemistry, aspartate aminotransferase (AST) was increased to 71 IU/L, alanine aminotransferase (ALT) 56 IU/L, Gamma Glutamyl Transpeptidase (GGT) 115 IU/L, and Alkaline phosphatase (ALP) 74 IU/L. Plain X-ray of abdomen revealed dilatation of transverse colon about 10 cm. An erect chest X-ray revealed gas under diaphragm (Figure 1).

Immediate fluid resuscitation and intravenous antibiotics were initiated. Upon admission, the patient was placed on ciprofloxacin and metronidazole. Hydrocortisone IV was initiated since the patient had a history of chronic prednisolone use and was given nothing-by-mouth. The patient underwent surgery after the diagnosis of peritonitis due to perforated viscera was made. Exploratory laparotomy revealed synchronous perforation of the sigmoid and hepatic flexure. After an effective abdominal washout, total colectomy was performed (Figure 2), followed by ileostomy. The rectal stump was left in place and oversewn. She was placed on enoxaparin 40 mg SQ every 12 hours for deep vein thrombosis prophylaxis.

On hospital day #2, patient was significantly improved with softened abdomen, improved leukocytosis, and increased urine output. On hospital day #3, the patient continued to improve with decreased abdominal distention and pain in addition to passing flatus per stoma. Oral diet was given 24 hours after removing the nasogastric tube on the third postoperative day. On the fifth day of her hospitalization, the patient was discharged in good condition on oral steroids and 5-ASA with a plan to perform ilerectal anastomosis 6 weeks later.

Discussion

The goal in treating any IBD flare is to induce remission of the acute flare, and design appropriate maintenance therapy to improve quality

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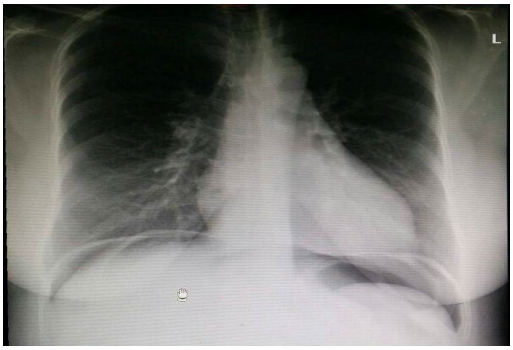

Figure 1: An Erect Chest X-ray Revealed Gas under Diaphragm.

Figure 2: Shows Specimen of Colon which was removed.

of life. Surgical intervention in ulcerative colitis is typically reserved for failure of medical therapy, acute change such as toxic colitis, perforation, bleeding, or the development of strictures or neoplasm [4].

Wilks and Moxon, in their description of ulcerative colitis, realized the danger of perforation, mentioning the cecum and rectum as possible sites where this was likely to occur [5]. It is now widely accepted that intraperitoneal perforation of the colon is the most lethal local complication of acute ulcerative colitis. Previous series in which the site of perforation is stated suggested that the commonest site is in the sigmoid colon [6-10]. Most of these series described solitary perforation. Presence of synchronous perforation, as in our case, is very rare.

The diagnosis of perforation in ulcerative colitis may be difficult to make. In the series of Edwards and Truelove, the presence of perforation was not recognized until autopsy in 10 of their 20 patients [11,12], and in the series of Dombal et al., there had been no preoperative clinical evidence of perforation in 5 of 11 patients who underwent emergency operation for sudden deterioration in their clinical condition [13]. In our case, high suspicion and presence of classical signs of peritonitis made the diagnosis not difficult.

Perforation of the colon may be preceded by dilatation of the colon although often perforation occurs without any such premonitory manifestation. In our case, the patient developed perforation in association with severe dilatation of the colon. Previous studies revealed high rate of mortality (50-80%) which related to comparatively longer patient histories of colitis, longer current attacks, slightly greater delays between presumed perforation and operation, and much higher transfusion requirements [14,15]. In our case, early diagnosis and intervention prevented those complications. In summary, we successfully managed a case of complicated UC via total colectomy and end ileostomy.

Conclusion

The possibility of free perforation in ulcerative colitis must be considered in fulminating cases. Careful clinical monitoring and early surgical intervention are crucial for quick, uneventful recovery.

Conflict of interests

Authors have no conflict of interests to disclose.

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Surgical Technique Open Access

Radical Neck Dissection: How We Do It?

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Abstract

Neck dissection is still considered a therapeutical surgical approach in the treatment of lymph node metastasis due to head and neck tumors. Radical neck dissections imply the "en bloc" removal of all the lymphatic tissue found in the lateral regions of the neck, including the sternocleidomastoid muscle, internal jugular vein and accessory nerve. During the years several variations of the original procedure have arisen, with the aim to reduce postoperative complications and morbidity, assuring a better quality of life, while preserving the same oncological efficacy. The presence of metastatic adenopathy lowers the patient's survival rate with approximately 50%. The surgical treatment of cervical adenopathies plays a crucial role in the future outcome of the patient's evolution. Although the current tendency is toward less radical types of neck dissections i.e. modified neck dissection, selective neck dissection, we still consider radical neck dissection as a trustworthy procedure in the treatment of head and neck tumors. Our aimwith this paper is to showcase the procedure, offer a technical description, underline its importance and emphasize some of the lessons we have learned during the treatment and follow-up of these patients.

Keywords: Head and neck cancer; Radical neck dissection; Surgical technique

Introducere

Evidarea ganglionară cervicală radicală reprezintă îndepărtarea "în bloc" a ganglionilor limfatici corespunzători regiunilor limfatice I-V ale gâtului, situați între fascia cervicală superficială și profundă, împreună cu mușchiul sternocleidomastoidian, nervul accesor și vena jugulară internă [1]. Conceptul de evidare ganglionară cervicală radicală a fost introdus pentru prima dată de George W. Crile, (1864-1943, Cleveland,Ohio) prima intervenție fiind efectuată în 1906. Mai târziu, în anii 1950, Martin Hayes este cel care utilizează sistematic metoda în tratamentul metastazelor ganglionare cervicale [2,3].

Tumorile primare care metastazează cel mai frecvent la nivel cervical sunt cele scuamoase, cu punct de plecare din căile aero-digestive superioare: cavitate bucală, orofaringe, hipofaringe, laringe, mai rar cele plecate din epifaringe, sinusuri paranazale, glande salivare [4]. Întâlnim și tumori secundare cu localizare cranio-cervicală având origine în diverse organe: piele, părți moi, os, glanda tiroidă, organe intraabdominale, plămîn sau sân [5].

Scopul acestui articol este de a prezenta indicațiile, contraindicațiile și principalele aspecte de tehnică chirurgicală ale evidării ganglionare radicale cervicale, așa cum este practicată în mod curent în serviciul nostru chirurgical (Clinica ORL, Universitatea de Medicină și Farmacie Tg. Mureș).

Evaluarea preoperatorie a tumorilor sau metastazelor cervicale

Diagnosticul tumorii primare, al adenopatiei sau al ambelor se poate stabili prin examinare clinică, laringoscopie, nazofaringolaringoscopie flexibilă, faringo-laringoscopie și esofagoscopie prin laringoscopie suspendată în anestezie generală, pasaj baritat esofagian, radiografie toracică, aspirație citologică de la nivelul adenopatiei, diverse metode imagistice-tomografie (CT), rezonanță magnetică nucleară (RMN), tomografie cu emisie de pozitroni (PET/CT), ecografie cervicală [6,7]. Histologia tumorii primare sau metastatice poate fi determinată preoperator prin puncție aspirativă și examen citologic sau prin biopsie excizională, ultima putând stabili și originea carcinomului scuamos i.e. tract aero-digestiv, nazo-faringian, carcinom tiroidian sau cancer al pielii [8].

Aspecte de tehnică chirurgicală

Din punct de vedere anatomo-chirurgical, disecția radicală respectă principial împărțirea compartimentală cervicală în cele șase regiuni descrise de Robbins și colab. [9]. Disecția radicală a gâtului în afecțiunile oncologice din sfera ORL se rezumă la compartimentele I-V, compartimentul VI făcând obiectul limfadenectomiilor din afecțiunile oncologice endocrine cervicale (tiroidă, paratiroidă) și fiind abordat doar electiv de către chirurgul ORL.

Majoritatea autorilor [10-12] notează între indicațiile frecvente ale disecției radicale cervicale următoarele: adenopatia metastatică voluminoasă, cu diametru peste 6 cm (N3) (Figura 1), multiple adenopatii omolaterale, bilaterale sau contalaterale, cu diametru între 3-6 cm (N2b, N2c), situate mai ales în vecinătatea nervului accesor, invazia extracapsulară a unor adenopatii ce prind nervul accesor și vena jugulară internă, adenopatii cu extensie extralimfatică, evidențiată imagistic, metastazele de la nivelul platismei sau pielii, recidivele sau metastazele persistente după evidare conservativă, iradiere, sau chimioterapie.

Între contraindicațiile metodei sunt notate: stadiul tumoral incipient (N0), prezența metastazelor la distanță, invazia tumorii la nivelul spațiului prevertebral, mușchiului scalen, mușchiului levator scapulae, plexului brahial, nervului frenic, mediastinului, bazei de craniu, invazia aproape circumferențială a carotidei comune sau interne (peste 270°), asocierea unor afecțiuni generale grave (cardiace sau pulmonare) ce nu pot fi compensate preoperator [10-12]. Dedivitis RA și colab. [13] consideră că limitele rezecabilității metastazelor cervicale

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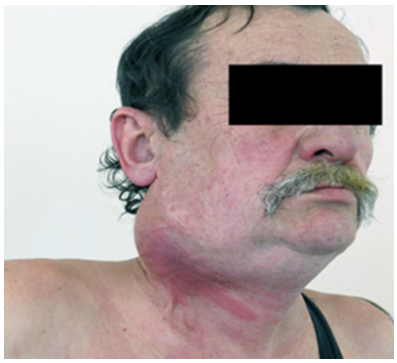


Figura 1: Adenopatie metastatică de dimensiuni importante (> 6cm), cu indicație pentru disecție radicală cervicală.

sunt reprezentate de invazia următoarelor elemente anatomice: artera carotidă comună, artera carotidă internă, fascia prevertebrală, invazia nervului frenic și a plexului brahial, mediastinul.

Incizia depinde de tipul intervenției, respectiv de localizarea tumorii primare; atunci când este indicată doar evidarea cervicală radicală preferăm incizia în crosă de hochei sau "lateral utility incision Lahey's" (Figura 2).

Inciziile în "Y", mai ales cele proiectate în apropierea carotidelor dar și inciziile ce creează lambouri înguste sunt de evitat. În situația în care este indicată și rezecția tumorii primare i.e. rezecție "en bloc" cu laringectomie, faringectomie sau glosectomie și evidare ganglionară cervicală radicală, modificăm incizia Gluck Sorensen utilizată în abordul tumorii primare completând-o cu incizia Lahey. Noi preferăm marcarea dermografică a inciziei și a principalelor repere anatomice dar și infiltrarea subcutanată cervicală cu ser fiziologic și soluție vasoconstrictoare pentru a facilita prepararea lamboului în planul subplatismal limitele acestei preparări fiind clavicula, mușchiul trapez, mandibula, linia mediană a gâtului. Nervul auricular mare și vena jugulară externă o păstrăm atașată mușchiul sternocleidomastoidian, pe care îl secționăm la origine deasupra claviculei (Figura 3).

Identificăm mușchiul omohioidian și secționăm pântecele posterior care intersectează vena jugulară internă, după care identificăm vena jugulară internă, carotida comună și nervul vag (Figura 4).

Se ligaturează vena jugulară internă cu 2 fire de mătase 2-0 însoțite de 2 fire transfixiante și se secționează după care se pătrunde prin disecție boantă sau digitală în țesutul grăsos supraclavicular până la fascia cervicală profundă și se vizualizează nervul frenic și plexul brahial (Figura 5).

Sunt ridicate elementele limfatice și non-limfatice situate pe traiectul mușchiului trapez, la nivelul fasciei cervicale profunde, secționându-se și ramurile nervului cervical superior, disecția avansând ulterior de-a lungul arterei carotide comune și nervului vag, până la bifurcația carotidiană (Figura 6).

Evidarea radicală a gâtului presupune sacrificarea nervului accesor, a venei jugulare interne, rezecate sub pântecele posterior al mușchiului digastric (pe partea lui medială) și a mușchiului sternocleidomastoidian, rezecat aproape de apofiza mastoidă (Figura 7A).

Alături de aceste "sacrificii" clasice se rezecă frecvent ramurile cutanate ale plexului cervical, glanda submandibulară, ductul Wharton, polul inferior al glandei parotide, nervul auricular mare, vena jugulară externă, artera și vena facială, mușchiul omohioidian (Figura 7B). Elemente anatomice păstrate (dacă este posibil) sunt: ramura marginală mandibulară a nervului facial, mușchiul digastric în întregime,nervul laringean superior, artera tiroidiană superioară, nervul lingual, nervul hipoglos, nervul vag, arterele carotide, nervul frenic, plexul brahial, ductul toracic. Plaga operatorie se spală cu soluție izotonică și se drenează aspirativ; pansamentul este simplu, necompresiv (Figura 8). Piesa postoperatorie este marcată și trimisă la examen histopatologic.

În cazul unor adenopatii avansate am fost nevoiți să practicăm evidarea ganglionară cervicală extinsă, când am sacrificat în mai multe cazuri artera carotida externă, nervul hipoglos, nervul vag, mușchiul digastric; intervențiile noastre nu s-au extins la rezecția arterei carotide comune sau arterei carotide interne. O provocare chirurgicală rămîn însă metastazele fixate de planurile profunde, recidivele, gâtul iradiat sau chimio-iradiat cu prezența de mult țesut cicatriceal [14-16].

Disecția radicală a gâtului nu este nici pe departe o tehnică chirurgicală anodină, complicațiile asociate direct metodei fiind și cele care limitează în opinia mai multor autori indicațiile acesteia [17-19]. Incidentele și accidentele intraoperatorii pot fi numeroase: hemoragie, reflex de sinus carotidian, pneumotorax, embolie gazoasă, trombo-embolism pulmonar, leziuni nervoase (lezarea ramurii marginile

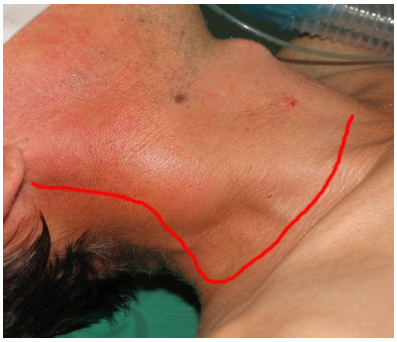


Figura 2: Incizie în „crosă de hochei" Lahey.

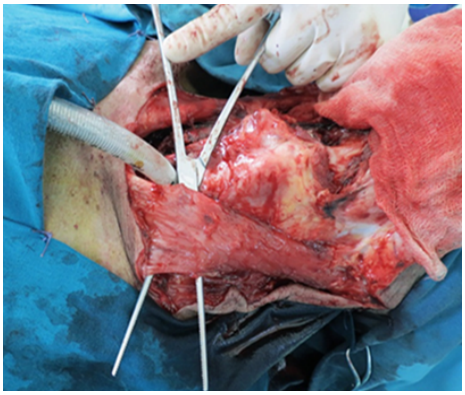


Figura 3: Secționarea mușchiului sternocleidomastoidian la origine după prealabila preparare a lamboului cutanat.

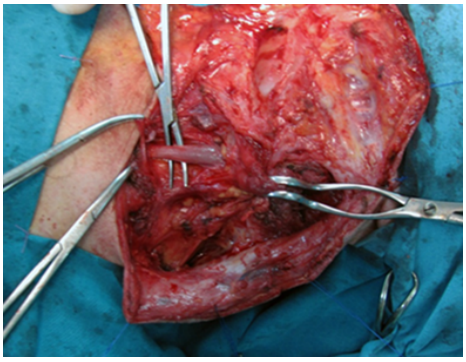


Figura 4: Identificarea arterei carotide comune, nervului vag și venei jugulare interne.

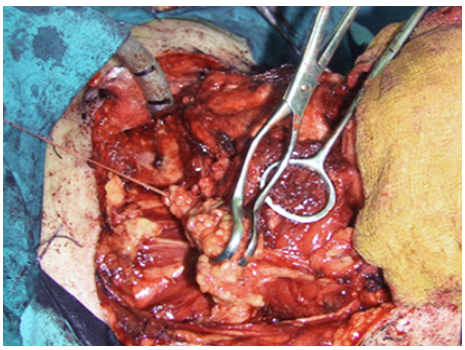


Figura 5: Disecția extinsă până la fascia cervicală profundă, cu vizualizarea nervului frenic și a plexului cervical.

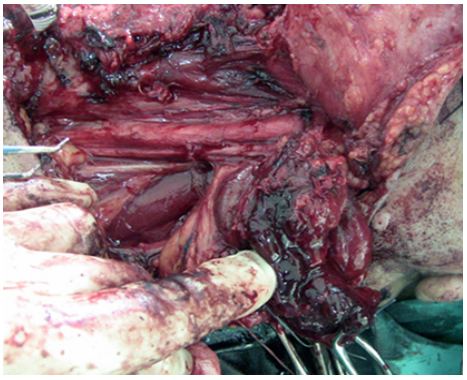
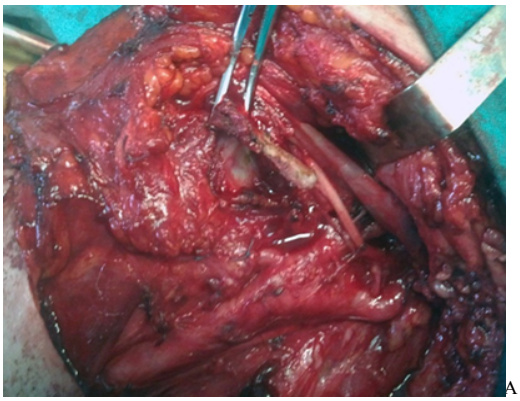


Figura 6: Excizia regiunilor limfatice și elementelor non-limfatice, la nivelul fasciei cervicale profunde, arterelor carotide și mușchiul trapez.



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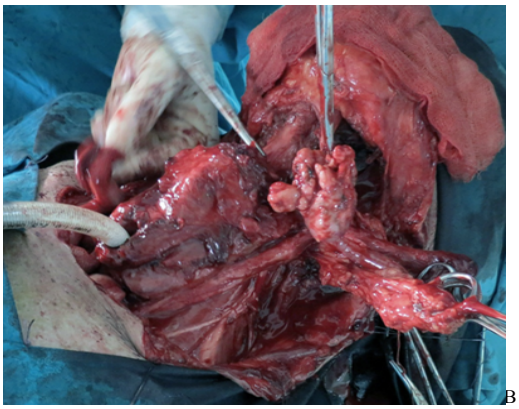

B

Figura 7: A) Secționarea mușchiului sternocleidomastoidian, polului inferior parotidian, venei jugulare interne, prepararea mușchiul digastric și a nervului hipoglos. B) Extirparea glandei submandibulare.

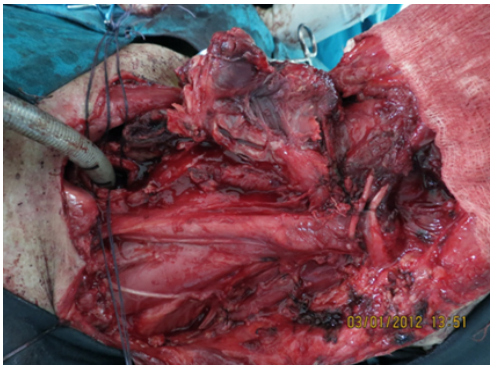

Figura 8: Aspectul final al unei disecții radicale cervicale.

mandibulare a nervului facial, lezarea trunchiului simpatic cervical, sacrificarea nervului accesor spinal, lezarea nervului hipoglos, rezecția nervului vag, leziunea plexului brahial), fistula limfatică. Pellini R și colab [18] și Campisi C și colab [19] notează următoarele complicații postoperatorii mai frecvent întâlnite: hematomul, infecția plăgii operatorii, necroza lamboului, fistula salivară, fistula limfatică, edemul facial, tulburări electrolitice, ruptura arterei carotide.

Concluzii

Prezența adenopatiei metastatice reduce la jumătate rata de supraviețuire a pacienților cu tumori maligne ale capului și gâtului. Din această perspectivă sancțiunea chirurgicală a acesteia joacă un rol crucial în îmbunătățirea prognosticul pe termen scurt și mediu al acestor pacienți. Deși nu putem să nu remarcăm tendința actuală către tehnici chirurgicale de limfodisecție cervicală mai puțin agresive, Țfuncționale, disecția radicală a gâtului rămâne în opinia noastră o tehnică cu bune rezultate în cazuri selecționate de tumori cervico-craniene, în special a celor din sfera ORL.

Conflict de interese

Autorii nu declară nici un conflict de interese.

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Cesarean Section: One of the Oldest and Controversial Surgical Procedures

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Abstract

The idea of the possibility of childbirth in another route than natural still exists from mythology. The name derives from the Latin "caedere" – cut, sever. For many centuries, ever since the Roman Empire, the operation was performed only rarely and women who died in childbirth. Indications that cesarean would be performed even women are living since 1040 in Rabbi Gershon to Metz, Talmud's comment. In 1581 the first paper appears in France dedicated caesarean women live, but the first successful Caesarean operation are reported in France, only in 1689 from surgeon Jean Rulau, in Ireland 1748 from midwife Marie Donaly and in 1794 in Virginia (USA) from the country doctor Jesse Bennett. Mortality after cesarean on women living it was still very high. A significant decrease occurred in the 19th century it when decline spectacular after improvements are made of the operation. Mainly this is due to Frank E. Polin in US, Alfred Kehrer in Heidelberg, Max Sänger in Leipzig and Eduardo Porro in Milan. Their refinements of the technique were essential cesarean bringing a lot of one that is currently running. Classical caesarean is practiced today after Stark technique, method Joel Cohen. After a long and controversial trend for nearly two millennia, marked for centuries by almost prohibitive mortality, the current cesarean operation is a great success in perseverance deeply humanitarian attempts to save two lives, a mother and child.

Keywords: Caesarean section; Morbidity and mortality; Surgical technique; History of medicine

S-au găsit datând încă din preistorie, schelete de femei care din cauza unor distocii grave de bazin au murit la naștere, iar fătul a rămas captiv în bazinul acesteia. Ideea posibilității aducerii pe lume a unui copil și pe altă cale decât cea naturală o aflăm încă din mitologie. Astfel, zeul Apolo ca răzbunare pentru infidelitatea iubitei sale pământene Coronis cu care zeul zămislise un copil, îi decide moartea. Înainte ca aceasta să fie cuprinsă de flăcări la incinerare, zeul, cuprins de remușcări, își extrage fiul încă viu din trupul mamei moarte. Acest fiu va fi Asclepios, zeul medicinei. Însuși Zeus și-ar fi extras progenitura, pe Dionisos, din trupul lui Semele, decedată înainte de termen. Din acest motiv, Dionisos a trebuit ca un timp, pentru a se matura, să fie ținut în coapsa lui Zeus. În mitologia persană, în "Cartea Regilor", se arată că prințesa Radabeh, soția lui Javal, având la naștere un travaliu lung și dificil, soțul acesteia cere ajutorul unei păsări mitice Simurg care îl învață cum să-și extragă copilul din abdomenul mamei. Acesta va fi Rostan, un erou legendar. În mitologia indiană, prințesa Maya l-ar fi adus pe lume pe Buddha direct din flancul drept al abdomenului. Brahma, s-ar fi născut și el direct din ombilicul mamei sale [1,2].

Într-un fel sau altul s-a observat totuși că viața unui făt putea fi salvată prin extragerea sa direct din abdomenul unei mame decedate la naștere. Nu întâmplător în anul 600 î.Hr., sub domnia lui Numa Pompilius (762-615 îHr.) s-a emis o lege "lex regia" (legea regală), prin care se interzicea îngropare unei gravide la sfârșitul sarcinii înainte de a i se fi extras fătul. Cel ce nu ar fi procedat în acest fel se arată în "Digesta" lui Justinian este considerat că a lăsat să se piardă odată cu mama și o speranță de viață. "Lex regia" a fost aplicată și sub domnia împăraților – a cezarilor sub numele "lex caesarea". Nașterea abdominală a primit și ea numele de "partus caesarea"[2].

Mult timp s-a crezut că numele de cezariană ar fi legat de cel al lui Iulius Cezar (100-44 î.Hr.) considerându-se că prin această operație ar fi fost adus el pe lume. Fapt inexact, deoarece mama lui, Aurelia, nu a murit la naștere, având ulterior și alte nașteri. O ipoteză preluată după Pliniu îl implică pe Publius Cornelius Scipio zis Africanul (235-183 Î. Hr.) a cărui mamă a murit la naștere, nereușind să-și aducă fiul pe lume. "A trebuit să i se incizeze abdomenul pentru a-l salva viu" arată Pliniu. Ulterior Scipio a primit numele de Cezar și e posibil ca operația să fi primit de la acesta numele de cezariană. S-a mai presupus că denumirea ar deriva din latinescul "caedere" – a tăia, a secționa [2].

Timp de multe secole operația s-a practicat foarte rar și doar pe femei decedate la naștere. Guy de Chauliac (1298-1382) recomanda la timpul său ca incizia să fie făcută în flancul stâng al abdomenului pentru a evita ficatul. În secolele 14 și 15 apar în Franța dar și în Orient, o serie de miniaturi și gravuri care ilustrează scene de extragere din abdomenul mamei decedate a unui făt viu. În secolul următor sunt autori cum de exemplu Suetoniu (1506), Charles Estienne (1545), Ronssens (1539), Ryff (1582) care, în tratatele lor, se referă și la această operație [2]. Ei îi discută indicațiile, sediul inciziei (mediană, în flancul drept sau curbilinie în stânga) precum și instrumentarul necesar. Între timp apar însă indicii că cezariana s-ar fi efectuat încă mai demult chiar și pe femei vii. În anul 1040 în comentarile la Talmud ale rabinului Gershon din Metz se susține acest fapt. În secolul 16 apar însă gravuri care vin să confirme ipoteza. Astfel în 1596 în cartea sa "La commare", Scipione Mercurio, anatomist și chirurg militar italian, probabil și mamoș, exemplifică cu imagini pozițiile ce trebuiesc date femeilor la naștere pentru cezariană; dacă starea femeii este bună, recomandă poziție semișezândă, bine sprijinită, iar dacă dimpotrivă femeia este foarte slăbită, poziție de decubit. Este însă puțin probabil

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ca Mercurio, călugăr fiind, să fi executat el însuși o astfel de operație. O gravură care ilustrează deasemeni sugestiv efectuarea cezarienei pe o femeie vie o găsim într-un tratat apărut postum în 1683 a lui Scultetus din Germania. Tot din această perioadă există însă și relatări directe de observații de cezariene realizate pe femei vii și ceea ce este surprinzător, cu succes atât pentru mamă cât și pentru copil. O primă relatare din 1581 aparține anatomistului elvețian Bauhin. El susține că în anul 1500 într-un canton din Elveția un anume Jacob Nufer care se ocupa de castrarea porcilor, disperat fiind că soția sa nu reușea să nască după un travaliu lung și obositor, cere permisiunea autorităților și intervine el însuși. Incizează abdomenul mamei din care extrage un copil viu; suturează apoi peretele. Soția a mai purtat și alte sarcini, iar copilul a trait mulți ani. O a doua observație de cezariană pe femeie vie datează din 1610. Ea a fost executată de doctorul JeremiahTrautmann din Wittenberg pe soția unui butnar, care, gravidă fiind, a fost lovită puternic în abdomen de un cerc de butoi. Chirurgul intervine și extrage un copil viu. După o perioadă bună, mama moare însă în a 25-a zi. Copilul a trăit până la 9 ani. E aproape incredibilă însă o relatare din 1647 în care soția gravidă, a unui fermier din Olanda, este împușă în abdomen de un taur înfuriat. Din plagă a putut fi salvat copilul viu dar mama a murit [3].

În 1581 apare în Franța prima lucrare dedicată cezarienei pe femei vii. Ea aparține medicului parizian Francois Rousset care a intitulat-o "Traite Nouveau de l'Hystérotomotokie ou Enfantement caesarien". În lucrare Rousset arată că "extragerea unui copil prin incizie laterală a abdomenului și a uterului la o persoană gravidă și care nu poate să nască altfel, nu prejudiciază viața nici a unuia nici a altuia și nu împiedică după aceea fecunditatea maternală". În tratat, autorul, care de fapt nu a executat personal această operație, îi dă numele de cezariană. El adună inițial un număr redus de observații, între care include și observația relatată de Bauhin. Într-o ediție ulterioară în latină, mai amplă, autorul adună noi cazuri. Avizul pentru publicarea cărții lui Rousset a fost dat de Ambroise Pare. A practicat el însuși împreună cu Jacques Guillimeau această operație pe un număr de cazuri dar având numai eșecuri își retractă susținerea [4].

Timp de aproape 2 secole cezariana pe femei vii nu a mai fost executată decât foarte rar: mortalitatea era de de 80-90%. Supraviețuirile constituiau o excepție. Se notează de exemplu o singură supraviețiure pe 24 cezariene. Cele mai multe femei operate mureau fie imediat de hemoragie, fie la o săptămână de infecție. Lipsa de reluare a tonicității uterului mai ales după un travaliu lung, favoriza hemoragia. Mult timp, plaga uterină nu a fost suturată. Abia în 1769, Lebas o suturează cu trei fire de mătase. Firele erau lăsate lungi, ieșind din plagă, pentru a putea fi scoase mai ușor. Infecția și peritonita erau inevitabile. Alain Espessat arată că la Paris în perioada 1740-1787 s-au înregistrat doar 6 succese față de 25 eșecuri. Mortalitatea, mai ales în clinicile universitare, ajunsese de necrezut, între 50 și 100%. Rarele succese se înregistrau mai curând în spitale mici sau chiar în mediul rural. Marii obstreticieni ai timpului practicau cezariana dar numai pe femei decedate. Foarte reticenți nu excludeau cezariana pe femei vii, arătându-i însă șansele minime. Ei stabilesc indicațiile cezarienei în orice situație, inciziile de preferat și instrumentarul necesar [4].

În fața numărului atât de mare de insuccese se constituie în 1791 la Paris o Societate anticezariană condusă de Jean Sacombe, societate care edita și un ziar propriu. Pe de altă parte se manifestă un alt curent din partea unor clerici foarte fervenți, ca de exemplu episcopul și inchizitorul de Sicilia F. E. Cangiamila, de a impune ca obligatorie cezariana pe femei moarte în vederea unui eventual botez al copilului. Regele Carol al III-lea al Spaniei emite în 1748 un edict prin care se oferă indulgențe în cazul efectuării unei cezariene sau dimpotrivă, amenințarea cu moartea în caz de refuz. În această perioadă atât de fierbinte asistăm totuși și la succese privind cezariana pe femei vii. În Franța în 1689 este realizată prima cezariană cu succes de către chirurgul Jean Rulau. Mama a supraviețuit dar copilul a murit după 2 zile. În Irlanda în 1748, moașa Marie Donaly execută cezariana printr-o incizie transversală, folosind un simplu brici. Ea sutureaza plaga cu ațe și ace aduse pe loc de la un croitor. Atât mama cât și copilul au fost salvate. Un dublu succes este înregistrat în anul 1794 în statul Virginia (SUA), când medicul de țară Jesse Bennett prectică cezariana pe propria soție în condiții de țară dintre cele mai grele, pe o masă improvizată, dar cu succes. Nu însemnă că mortalitatea după cezariene pe femei vii nu era încă foarte mare. O scădere importantă a acesteia s-a produs abia în perioada imediat premegătoare secolului 19 când scade spectaculos de la 80 la 22%. Aceasta se produce când încep să fie aduse îmbunătățiri ale operației. În 1882 Frank E. Polin din SUA execută sutura plăgii uterine cu fire de argint. La fel s-a procedat și în alte 16 cezariene. O scădere cu totul importantă a mortalității se produce însă în sec. XIX când ea ajunge la 8 și chiar 3%. În principal aceasta se datorează unor doi mari pioneri: Alfred Kehrer din Heidelberg și Max Sänger din Lepzig. Perfecționările lor privind tehnica cezarienei au fost esențiale apropiind-o mult de cea care se execută în prezent [2,5].

Alfred Kehrer recomandă ca incizia uterină să fie transversală, segmentară, urmată de o sutură cu multă grijă și totul în condiții de asepsie. El practică această operație la 25 septembrie 1881, noapte în condiții grele de țară dar obținând un dublu succes. O a doua operație efectuată în clinică universitară a fost în schimb un total eșec. Max Sänger este cel care 1882 a mai practicat cezariana prin incizie corporeală longitudinală clasică. Suturează uterul cu fire de argint. Tehnica a fost urmată cu succes în același an de Leopold și în Franța, de Bart în 1884.

Propuneri pentru efectuarea unei incizii segmentare joase a uterului au fost făcute cu mult înainte. Printre aceștia se înscriu R.W. Johnson în 1780, Osander în 1805, Rigen în 1820 sau J. A. Baudeloque în 1823. Propunerile nu au fost însă luate în seamă. O altă propunere deasemenea neaplicată o face în 1819 Charles Bell. El recomandă o incizie mică pe segmentul inferior al uterului și care să fie lărgită prin dilacerare digitală. Ideea a fost reluată de Blundel în 1834 dar fără succes. O operație care a făcut epocă a fost realizată în 1876 de Eduardo Porro din Milano. În cursul cezarienei la o gravidă de 25 ani cu bazin rahitic foarte îngust, Porro este confruntat cu o hemoragie uterină de nestăpânit. Sub hemostază provizorie a uterului el practică odată cu cezariana și histerectomie subtotală salvatoare atât pentru mamă cât și pentru copil. Operația îi va purta numele. Succese au mai fost obținute în 1879 în Franța de Fochier si Tarnier. Un număr de ani, cezariana Porro a fost efectuată în paralel cu cezariana clasică, dar mortalitatea foarte mare chiar și de 50% a făcut să fie părăsită [4].

Cezariana clasică este practicată azi după tehnica Stark, metoda Joel Cohen cu incizie suprapubiană și histerotomie segmentară transversală joasă.

După o lungă și controvesată evoluție de aproape două milenii, marcată timp de secole de o mortalitate aproape prohibitivă, cezariana actuală reprezintă un mare succes în perseverența încercărilor profund umanitare de a salva două vieți, a mamei și a copilului în situația unor dificultăți majore la naștere. Beneficiul pentru mame s-arătat enorm, mai ales că cezariana a ajuns să constituie astăzi o operație din cele mai sigure cu o mortalitate de 0,012% [5]. S-a ajuns ca în unele medii sociale să se manifeste din partea femeilor gestante o tendință preferențială, nu întotdeauna justificată, pentru nașterea prin cezariană, operație care în trecutul îndepărtat era practicată doar în condiții extreme.

Conflict de interese

Autorii nu declară niciun conflict de interese.

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