Journal of Blood & Lymph
ISSN: 2165-7831

Lorant et al., J Blood Lymph 2016, 6:1
DOI: 10.4172/2165-7831.1000144

Research Article Open Access

Rectal Cancer and Invasion of Veins: Importance in TNM Staging 2

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Abstract

Summary: Accurate information about infiltration of the tumor to the various layers of the rectal wall is important.

Material and methods: A histopathological study of surgical specimens from 351 surgical specimens from patients with adenocarcinoma of the rectum revealed invasion of veins by primary growth in almost 52%.

Results: Follow-up studies showed that the corrected 5-year survival rate was significantly worse and liver metastases developed more frequently when venous invasion was present.

Invasion of extramural veins was particularly significant whereas spread confined to intramural veins was less important. Invasion of large (thick–walled) veins was of greater consequence than invasion of small (thin-walled) veins and spread into thick–walled extramural veins, had greatest adverse influence of all.

Venous spread of tumor takes place in parallel with local spread as measured by the Dukes' stage but exerts an influence on prognosis independent of the Dukes' stage.

Similarly, veins invasion parallels the number of lymph nodes metastases but appears to exert an independent influence on prognosis.

Conclusion: The venous spread provides a precise assessment of the likely behavior of rectal cancer, but does not replace indices such as the Dukes' stage, or the number of lymph nodes metastases in use.

Keywords: Dukes' stage; Rectal cancer; Vein invasion

Introduction

Once a diagnosis of rectal cancer has been confirmed histologically, preoperative staging is mandatory to assist therapeutic decision making [1].

Today, several imaging modalities of great potential exist for local staging, including three-dimensional reconstruction [2-4]. The value of these techniques has been expressed as a correlation between the pretreatment tumor stage (CT) and the corresponding pathological stage (PT), the latter being regarded as the "gold standard".

Accurate information about infiltration of the tumor to the various layers of the rectal wall is important if local excision is anticipated [5]. The best modality with an acceptable accuracy for determining invasion into the layers of the bowel wall is end rectal ultrasonography [2].

Since the initial report by Brown and Warren in 1938 demonstrating an increase in visceral metastases on patients with rectal cancer with vascular invasion, a number of investigators have examined the influence of vascular invasion by tumor in colorectal cancer. They are two type of vascular invasion: blood vessel and lymphatic vessel invasion [5]. One would predict the presence of vascular invasion to be associated with an increased incidence of lymph nodes metastases and distant dissemination and with a decrease in survival [6].

Differences in the definition of vascular invasion, the methods of detection, and perhaps, the metastatic potential of the cells once they have gained access to blood and lymphatic vessels may explain, in part, some of the variations observed [7].

Surgical removal of the rectum by either synchronous combined excision or anterior resection with TME or Partial Mezorectum Excision (PME).

In an autopsy review they found that visceral metastases developed in two-thirds of cases in which there was venous invasion, but in no case in which venous invasion was not seen. In some studies the presence of carcinoma cells was found in the peripheral blood in 8 of 15 cases with histological evidence of venous invasion in the surgically excised specimens of rectum.

In other studies the authors suggest that invasion of veins may occur without being histologically demonstrable [8].

An important issue raised by Quirke and Morris is the recommendation to use the fifth rather than the sixth edition of TNM. When dealing with venous invasion and tumor nodules/deposits in the pericolorectal adipose tissue of a primary carcinoma, without histological evidence of residual lymph node [9].

Compared the staging methods, the Astler-Coller stage and the presence or absence of BW (blood vessel invasion) is the most significant correlation with survival, in patients with lymph node metastases [10].

Patients and Methods

The histological sections from 351 operation specimens from patients operated on for cure of carcinoma of the rectum between 1992-2007 were reviewed giving particular attention to the presence and extent of any invasion of veins: invasion of veins outside the

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Received July 20, 2015; **Accepted** December 20, 2015; **Published** February 10, 2016

Citation: Lorant K, Roland K, Denisa M (2016) Rectal Cancer and Invasion of Veins: Importance in TNM Staging 2. J Blood Lymph 6: 144. doi: 10.4172/2165-7831.1000144

muscle of the rectal wall was classified as extramural venous spread, while invasion of veins in the submucoasa or muscular is propria only was classified as intramural venous spread. The thickness of the wall of any invaded vein was also voted: veins with thick walls containing a well-developed smooth muscle layer were classified as "thick-walled", whereas veins which were more sinusoid in nature with thin walls containing little or no muscle were classified as "thin-walled".

The Dukes' stage and the number of lymph nodes that contained metastases were also recorded in each case.

Because of the large volume of histological and clinical data, the information was transferred into computer punch cards for analysis (SPSS-Chicago). The statistical significance of results was assessed using the x^2 test.

Results

Of the patients who died the cause of death was confirmed by autopsy in only 17 cases, but liver metastases were found at primary operation or at subsequent laparotomy in 44 cases.

Liver metastases were assumed in 27 patients who had clinically enlarged knobbly liver and in a further 7 patients with a history of weight loss with jaundice before death.

Incidence of venous invasion

Evidence of invasion of rectal veins by tumor was found in 182 of the 351 cases (51.9%), fully studied and, as Table 1 shows, in over two-thirds of these extramural veins were involved (127 36.0 %) (Table 1).

Venous invasion and Dukes' staging

The incidence of venous invasion increased with the Dukes' stage 20% in stage A, 47% in stage B and 64% in stage C (Table 2).

Of the 9 stage A lesions in which venous spread was demonstrated only 1 (5%) involved extramural veins.

In contrast, when tumor had breached the bowel wale the incidence of extramural venous invasion was higher and was not influenced by lymph node status (70% and 75% for stage B and C respectively).

Liver metastases and venous invasion

Liver metastases and death have an overall incidence 25% (Table 3).

A low incidence of liver metastases was observed in patients in whom venous invasion was not demonstrated, in comparation with patients in whom venous invasion had occurred (14% and 35% respectively, $p<0.001$).

In the latter group, liver dissemination were less common in preserve of venous invasion to the rectal wall (intramural), compared with extramural venous spread (23% and 40% respectively).

The type of extramural venous invasion and liver metastases is show in Table 4.

Liver metastases were present in 57% of cases in which thick–walled extramural veins dissemination was present ($p<0.001$).

The survival in 351 patients

The overall 5 year survival rate of the 351 patients was 57%. From this survival rate are excluded all patients who died in the immediate preoperative period of 4 weeks (Table 5).

In cases that the venous invasion was not demonstrated, the corrected 5 year survival rate was 73%.

The survival rate when venous invasion was combined to the bowel wall (66%) did not differ significantly from when venous invasion was not demonstrated ($0.2<p<0.5$), but in presence of extramural venous invasion the corrected 5-year survival rate was halved to 33% ($p<0.001$).

Table 4 shows the type of extramural venous invasion and survival rate. In this table, the corrected 5-year survival rate in presence of invaded extramural veins with thick-walled vessels was only 19%, less than half then thin-walled extramural veins were involved ($p<0.001$) (Table 6).

The combined effect on the corrected survival rate of the venous invasion and the Dukes' invasion had no significant effect on survival in stage A category cases, but the presence of extramural venous invasion is associated a decrease in survival in B and C stage growths. The special situation was observed in stage C category, in these cases the presence of thick–walled extramural veins invasion was associated with only 8% survival, but even in the presence of the extramural veins invasion only

Venous invasion	No	%
Not present	169	41.1
Present	182	51.9
-Intramural	55	15.8
-Extramural	127	36
Total	351	100

Table 1: Venos invasion in surgical specimens of rectal cancer.

Dukes' stage	Present %	Intramural only	Extramural only
		N/%	N/%
A	9	9	1
(n = 47)	-20	-95	-5
B	62	18	44
(n = 132)	-47	-40	-70
C	110	26	83
(n = 171)	-64	-25	-75

Table 2: Dukes' stage, venous invasion of rectum carcinoma.

Venous invasion	Total	Number with liver metastases	%
Not demonstrated	169	24	14.2
Present			
-Intramural	55	13	23.4
-Extramural	127	51	40.2
All cases	351	88	25

Table 3: Liver metastases in rectal cancer patients, and venous invasion.

Invaded extramural veins	Total	Number with liver metastases	%
Thin-walled	80	24	30.4
Thick-walled	47	26	57

Table 4: Extramural venous invasion and liver metastases.

Venous invasion				
	Not demosntrated	Present		Total
		Intra/Extra		
Patients survivors after first 4 weeks	164	54	124	342
5-year survival	103	30	35	168
Corrected 5 year survival rate (%)	73	60	33	57

Table 5: Patients with rectal cancer, and survival rate; and venous invasion.

Invaded extramural veins	Survivors after surgery	5-year survivors	Corrected 5-year %
Thin-walled	78	28	41
Thick-walled	45	8	19

Table 6: The extramural venous invasion and survival rate.

Venous invasion	Dukes' stage and 5 year survival rate %		
	A	B	C
Not demonstrated	48	43	23
Present			
-Intramural	51	42	20
-Extramural			
Thin-walled	-	68	23
Thick-walled	0	52	8
Total	96%	78%	31%

Table 7: Survival rate, venous invasion Dukes' stage.

Number	Survival after surgery	Nr. of 5 years survivors	Corected 5-year survival rate (%)	p.
1-3 lymph node (NL) metastases				
Not demonstrated	38	20	29	<0.05
Intramural	17	5	20	0.2
Extramural	35	9	15	<0.001
Total	90	68%	43%	
≥ 4 NL metastases				
Not demonstrated	21	4	12	<0.02
Intramural	9	3	21	0.1
Extramural	43	3	4	<0.001
Total	73	22%	17%	<0.001

Table 8: Survival rate, lymph node metastases, and venous invasion.

in the thin–walled vessels the survival rate was halved in comparation with when venous invasion was not demonstrated (Table 7).

In Dukes' tumors the corrected 5-year survival rate is less than 43% when less than four lymph node metastases were present (Table 8).

In this group (stage C) of cases with few lymph node metastases, the 5-year survival rate was considerably higher (59%) when venous invasion was not present. In presence of extramural or intramural dissemination in veins the corrected survival rate was lower of 30%.

In presence of four or more lymph modes metastases the corrected 5-year survival rate was 17% and in presence of extramural venous dissemination in these cases the survival rate was 8%.

Discussion

Horn et al. found that Blood Vessel Invasion (BVI) was an independent prognostic factor for distant metastases but not for survival [5].

The presence of venous invasion in associated with an increased risk of the future development of distant metastases (particularly hepatic) and cancer–related death [11-14].

Since the 1990s, several authors have investigated the clinical implications of extramural tumor deposits with no residual LN structure in colorectal cancer [15,16].

In same studies two types of BVI are described. Invasion of blood vessels within the bowel wall is defines as intramural BVI and invasion of blood vessels outside the bowel wall (per colonic fat or subserosal fat) is defined as extramural BVI invasion [17-19]. Both Talbot et al. [9] and Minsky et al. [6] found that the extramural component of blood vessel invasion was not predictive of survival.

The observation of BVI in 51.9% of cases of carcinoma of the rectum is a rather higher incidence than previously reported from others.

The result from the present study indicates that there is a significantly lower survival rate when venous invasion and venous spread is observed. This is evidently because tumor spread by the blood stream is a consequence of venous invasion [19-22]. Liver metastases developed over twice as frequently in patients with venous invasion as in those in whom it was not demonstrated.

Dissemination into extramural veins for a more pronounced effect of on liver metastases formation and survival rate than invasion of intramural veins only [23-24]. The difference between intramural venous invasion and not demonstrable VNI with regard to liver metastases and to 5-year survival is not statistically significant [25-27]. Some studies shown that when such invaded thick–walled veins lie outside the rectal wall there is particularity poor prognoses [28-30].

The present study suggests that the correlation of extend of VNI and the Dukes' stage shown that local spread proceeds in parallel with venous invasion, but venous spread (Table 7) exerts an influence in progress independent of the Dukes' stage.

Correction studies on the presence or absence of lymph node metastases based on imaging report a low predictive value. However, the question remains of how important this is, as there are only two circumstances is which the presence of lymph node metastases is relevant in clinical decision making: first, the choice of local excision in the absence of lymphadenopathy and second the present of lymph node metastases outside the end pelvic envelope makes the primary tumor locally advanced [31-33]. In this first situation the histological characteristics of the primary tumor are now relevant than lymph node imaging [34-36].

The results of this study provide such an indication by demonstrating that venous dissemination of rectal cancer is directly related to the development of liver metastases, and this observation is in concordance with other publications [37-39]. Our results demonstrate that the spread of cancer of the rectum into veins is of the greatest importance in the natural history of the disease, possibly more important than lymphatic spread.

The Dukes' staging is a remarkably consistent index of prognosis, for a minimal amount of extra attention to histological details its usefulness, still further increased.

The presence of VNI in Dukes' classification with extramural veins invasion significantly reduce the 5-year survival rate of stage B and C cases, and when thick–walled extramural veins are invaded the prognosis is particularly poor.

The importance of venous spread carries implication for surgical technique in the treatment of rectal cancer and provides a rational basis for early ligation of the superior hemorroidal vein, as advocated by Moynihan.

Our results lend weight to the theoretical considerations by showing that veins are invaded by tumor in over 50% of cases of rectal cancer and malignant emboli are likely to be released by operative manipulation in these cases [40-42].

Preoperative chemo radiotherapy (CRT) is used in the management of locally advanced rectal cancer to downsize tumor bulk and reduce the risk of local pelvic recurrence [43-45].

In some studies, 35% of patients had a complete pathologic response after neoadjuvant CRT. More than 3% of patients are metastatic disease within the mesorectal lymph node despite achieving PCR of the primary tumor [46-49].

In our study, the rate of metastatic deposits within nodes increased proportionally with T stage.

Quirke and Morris published in Histopathology [28], about the guidelines for the reporting of surgically resected specimens of colorectal cancer [9]. The authors state that 15-18 LM are usually recovered in the best centers and this number is advisable for all pathologists [1]. However, there is no general consensus given that other authors, reporting colorectal cover guidelines, have recently proposed a mean number of 12-15 LNs [50].

In a large series of colorectal cancers reported by Goldstein, about 30% of pT3N+ patients had a single metastatic lymph node (LN) and the percentage of specimens with one LN metastases increased from 41.62% to 80.36% when the number of LNs increased from 11-15 to >21 LN.

Conclusions

Observation of venous spread provides a precise assessment of the likely behavior of rectal carcinoma, but does not replace the Dukes' stage, TNM and/or the number of lymph nodes metastases in routine use.

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