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Recurrence pattern of rectal cancer after surgical treatment. Analysis of 122 patients in a tertiary care center

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ABSTRACT

Survival in rectal cancer has been related mainly to clinical and pathological staging. Recurrence is by far the most challenging issue when surgical treatment of rectal cancer is concerned. This study aims to establish a recurrence pattern for rectal adenocarcinoma submitted to surgical treatment between March 2003 and July 2016. After exclusion criteria were applied, one hundred twenty two patients were analyzed. Global recurrence was found in 22% of them, while 13.1% have had local recurrence. Disease-free survival was 23.9 months, in average, and medium follow-up was 34.13 months, varying from 6 to 115 months. Recurrence, in literature, is usually between 3 and 35% in 5 years, and shows a 5-years survival rate of only 5%. Around 50% of cases, recurrence is local, confined to pelvis. This data followed literature in most aspects evaluated, although finding a high rate of local recurrence remains a challenge in the seek for better surgical outcomes.

Padrão de recorrência de câncer retal em seguida ao tratamento cirúrgico. Análise de 122 pacientes em um centro terciário

Palavras-chave:
Recorrência
Câncer retal
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RESUMO

A sobrevida de pacientes com câncer retal tem sido relacionada, sobretudo, aos estadiamentos clínico e patológico. De longe a recorrência é o problema mais desafiador, no que concerne ao tratamento cirúrgico do câncer retal. Esse estudo pretende estabelecer um padrão de recorrência para pacientes com adenocarcinoma retal submetidos a tratamento cirúrgico entre março de 2003 e julho de 2016. Após a aplicação dos critérios de exclusão, foram analisados 122 pacientes. Recorrência global foi constatada em 22% dos pacientes, enquanto que 13,1% tiveram recorrência localizada. A média para sobrevida livre de doença foi de 23,9 meses, e o acompanhamento médio foi de 34,13 meses, com variação entre 6-115 meses. Na literatura, em geral a recorrência se situa entre 3-35% após 5 anos, com um

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percentual de sobrevida após 5 anos de apenas 5%. Em cerca de 50% dos casos a recorrência é localizada, ficando confinada à pelve. Os presentes dados acompanharam os achados da literatura na maioria dos aspectos avaliados, embora o achado de elevado percentual de recorrência localizada permaneça ainda um aspecto desafiador na busca de desfechos cirúrgicos mais satisfatórios.

Introduction

Colorectal cancer (CRC) is third more frequent non-melanoma neoplasm in Brazil and fourth in the world. Approximately one million new cases per year are diagnosed. Rectal carcinoma is responsible for 30–57% of all colorectal cancers. Mortality rate is estimated in up to 50% per year, and 5-years survival rate for all stages is about 70%.[1–6]

In Brazil it has been estimated for 2016–2017 a total of more than 34,000 new CRC cases, being 16,660 men and 17,620 women.[7]

In the last decades there has been a decrease in mortality and morbidity rates in CRC patients, probably due to better diagnosis, polyp biology understanding and removal, pre and post-operative care and staging, surgical technique, pre-operative staging and neoadjuvant/adjuvant therapies. Oncological results, however, have not grown this good, keeping survival rates close to what used to happen decades ago.[8,9]

Survival and disease-free survival in CRC has been related to many clinical, pathological, molecular, and genetic factors. This is why issues like early diagnosis, patient age, tumor location, histology, depth of invasion, lymph node invasion, levels of carcino-embriogenic antigen (CEA) and genetic expression gain importance when concerning evaluating prognosis.[10,11] Above all this factors, pathological analysis of the surgical specimen is the most relevant information in order to establish prognosis.

Concerning surgical technique, the one most important technical detail in rectal cancer surgery is total mesorectal excision (TME), whereas other concepts like high ligation of mesenteric vessels and lateral pelvic dissection remain object of frequent debate.[8,10,12,13]

Every healthcare professional dealing with rectal cancer treatment is still challenged by both local and metastatic recurrence which is by far the most import concern. It is responsible for a high morbidity and mortality. The best treatment that has also shown the best results in rectal cancer treatment includes neoadjuvant therapy when indicated, excision of rectum, together with mesorectum (TME), and adjuvant therapy, when needed.[14–17]

Rectal cancer recurrence is local in more than 60% of recurrences,[4,18] independent of low anterior or abdomino-perineal resection, and in about 50% of all recurrences, there is no tumor in any other organ. Local (or pelvic) recurrence after curative-intention surgery is an important cause of morbidity in these patients' follow-up. Three to 35% of patients operated of rectal cancer will have local recurrence.[4,14,19] Which has been shown to follow mainly surgeries with inadequate pelvic dissection, incomplete TME removal and affected surgical margins, but advanced stage tumor, tumor perforation and surgeon's experience can also count for it.[14]

Objective

Demonstrate the epidemiology and profile of patients submitted to surgical treatment of rectal carcinoma in a single surgical group, and analyze the recurrence pattern.

Methods

Data from patient files and from a database used to manage colorectal cancer patients were reviewed. All patients are from "Dr. Mario Gatti" City Hospital, a tertiary care facility in Campinas, SP, Brazil. Inclusion criteria were all patients submitted to surgery considered curative for primary rectal carcinoma, from up to 14 cm distant from anal verge, measured either by digital examination, rigid proctoscope or magnetic resonance images; and who had at least 6 months follow-up after surgery.

From an initial group of 134 patients, 12 were excluded from study because of metastatic disease (no matter whether resected or not) found at first surgery. Period of study was from June/2003 to July/2016. The following variables have been studied: age at surgery, gender, follow-up time, neoadjuvant therapy, adjuvance, histopathological features, TNM classification, recurrence and time for recurrence after surgery. Data is shown within simple frequency tables and graphics.

Results

From a group of 122 patients, 68 (55.7%) were female and 54 (44.3%) male. Rectal cancer occurred in this group from 23 to 86-years-old, with an average of 60.2 years (Fig. 1).

TME was performed in 113 patients, being 79 (64.7%) low anterior resection (LAR), 25 (20.5%) abdomino-perineal resection (APR), total proctocolectomy in 8 (6.5%) and 1 (0.8%) pelvic exenteration. The remaining 9 patients (7.4%) were treated with local resection. Open or laparoscopic surgery was chosen based on patient clinical conditions and laparoscopic equipment availability.

Every tumor described as pelvic, or below peritoneal fold, except for those elected for primary local excision, received neoadjuvant chemoradiation. The others did not get neoadjuvant treatment and went straight to surgery. All patients classified as T2 and T3 received radiotherapy at a total dose of 4500 cGy, during 5 weeks (180 cGy/week day). Chemotherapy

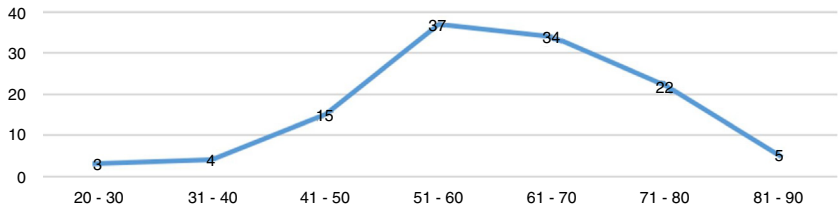

Fig. 1 – Age at diagnosis of rectal cancer.

schema during neoadjuvant therapy was elected based on patient status and drug availability, and was one of the following three options: fluouracil beginning with radiotherapy from day one to day 5 and from day 20 to day 25; fluouracil once a week during the 5 weeks of radiotherapy; or oral capecitabine during the 5-weeks radiotherapy. Surgery was performed from 4 to 12 weeks after neoadjuvant chemoradiation ending.

Tumor classification evaluating depth of invasion, lymph nodes disease and distant metastasis, based on TNM staging, 7th edition[20] was obtained after surgical specimen analysis, and result is shown in Table 1. Most of them were T3 and N0, showing a high incidence of advanced disease in the studied group. All T2 and T3 have gone through neoadjuvant therapy, at least 4 weeks before surgery. Tumor differentiation has also been assessed. Two patients (1.6%), had poorly differentiated tumor, while 83 (68%) were moderately differentiated and 9 (7.3%), well differentiated. In 19 patients (15.6%) there was complete pathological response after neoadjuvant therapy. The remaining 9 patients (7.3%) have had this information omitted in pathological report.

All patients were oriented to return periodically to a follow-up medical appointment, when routine exams were done. Routine follow-up includes digital rectal examination, thoracic and abdominal computed tomography (CT) scan, pelvic CT and/or magnetic resonance image (MRI), carcino-embryogenic antigen (CEA), colonoscopy and positron-emitting tomography (PET-CT) when needed. Minimum follow-up period is 6 months, and up to 115 months, with average of 34.1 months.

Table 1 – TNM classification (AJCC – 7th edition).

	N	%
T		
T0	19	15.6%
Tis	03	2.5%
T1	08	6.5%
T2	28	23%
T3	58	47.5%
T4	06	4.9%
N		
Nx	03	2.5%
N0	84	68.8%
N1	30	24.7%
N2	05	4%
G		
Poorly differentiated – G3	02	0.6%
Moderately differentiated – G2	83	68%
Well differentiated – G1	09	7.4%

Nineteen (70%) of all recurrences were found in patients with T3 tumors. One patient recurred from a tumor in situ, 4 (14.8%) from T2 and 3 (11%) from T4 tumor. No T1 tumor recurred in this series. Nineteen recurrences (70%) occurred in patients with no lymphatic invasion (N0), while N1 were responsible for 8 recurrences (29.6%) and no patients classified as N2 had recurrence (Fig. 2). Margins were not free in 2 patients with recurrence.

Twenty-seven patients (22%) have had tumor recurrence in any moment during post-operative follow-up. Local recurrence, associated or no with other recurrence was 13.9% (17 patients). When only local recurrence was considered, with no other metastasis, 12 patients were found. Within this group, 6 had lung metastasis and in one case, lung and liver metastasis at the same time. Three patients had lung only disease, 4 (3.2%) had bone metastasis (2 in the spine), and 2 had both lung and liver metastasis (Fig. 3). Six from eight patients (75%) who developed recurrence and had positive nodes on first surgery, have developed distant metastasis, and 3 of them associated with pelvic recurrence.

Recurrence occurred from 5 to 68 months, and the average disease-free survival in these 16 patients is 23.9 months (Fig. 4).

Discussion

Colorectal cancer is a highly prevalent disease, therefore, the quest for better results is an actual challenge.[8,9] Due to importance of surgical technique in the rectal cancer prognosis, quality of procedure has been widely emphasized, specially considering total mesorectum excision, and a great importance has been given to short and long-term results in colorectal cancer treatment centers, aiming to define ideal quality criteria in rectal cancer surgery. One of the most important criteria to establish excellence in rectal cancer treatment is the recurrence rate, being local recurrence or distant metastasis.[10,14,19]

In this series, where 122 patients were treated of rectal cancer with curative intention, female were more prevalent (55.7%), and this data does not show the same as literature, where most series show more men than women diagnosed of rectal cancer. Average age on diagnosis was however coincident with other series.[6,21]

Majority of surgeries for rectal cancer treatment was low anterior resection (64.7%), and APR has become rare over the years. New surgical concepts, techniques, equipment and neoadjuvant therapy has made it an exception, not only in this series, but in all literature.[8,14,15,22]

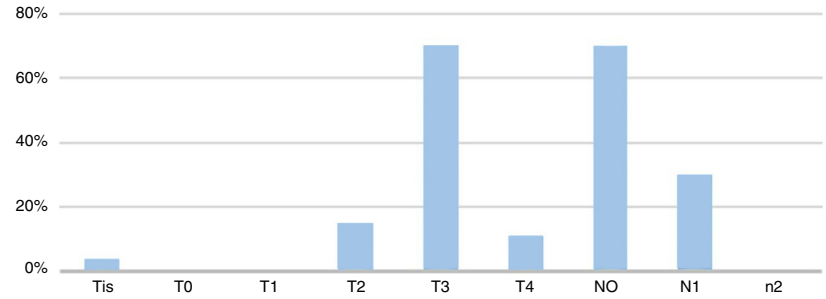

Fig. 2 – Recurrence X T/N stage.

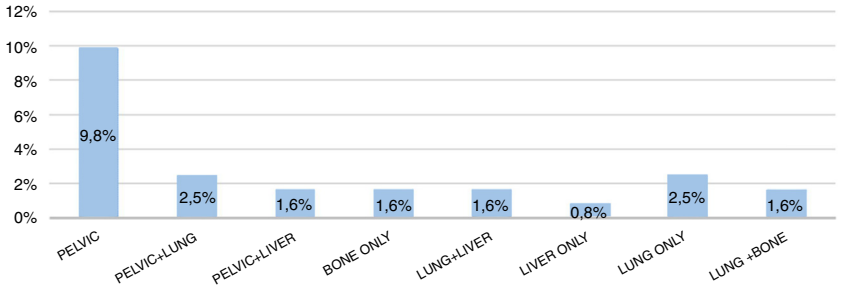

Fig. 3 – Site of recurrence.

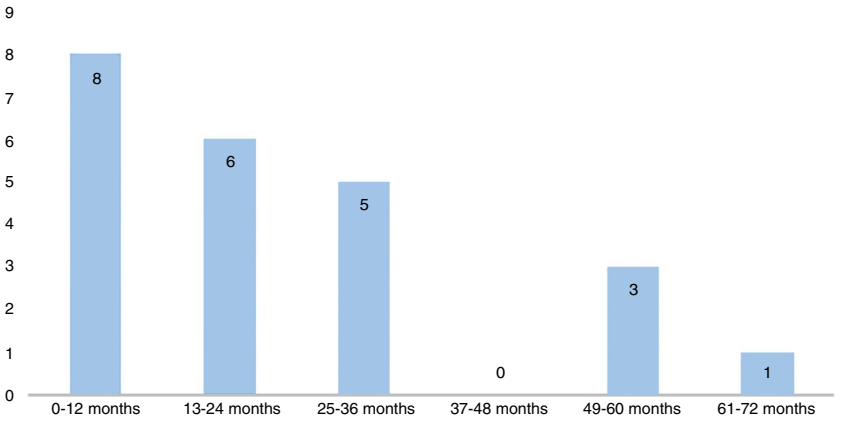

Fig. 4 – Time to recurrence after surgery.

In the first years of evaluation – from 2003 to 2010, timing of surgery was after 4–6 weeks after completing chemoradiation, and from 2010 to now, it is no shorter than 8 weeks. Total pathological response and local recurrence are object of study around the world in bigger series regarding timing of surgery after chemoradiation.[11,23,24] However, there is no study on this topic here due to a small number of subjects, and hence, lack of statistical relevance.

Except for those patients who undergone local excision, surgery was always performed using total mesorectum excision (TME) principle, and other organs were excised when tumor invasion was present (T4 tumors), mainly vagina, bladder and seminal vesicles. However, lateral pelvic dissection has never been an issue to pursue, as its importance in postoperative morbidity and rectal cancer local recurrence is still under debate between eastern and western world.[25–28] Hopefully in a near future this issue can be totally cleared for the best technique to be chosen.

T3 and T4 tumors are of high risk of death, when compared with T1 and T2. Depth of invasion is highly related to prognosis.[3] In this series majority of patients were in advanced disease, showing that diagnosis must be done earlier if a better outcome is wanted. Despite a late diagnosis is shown here, it concurs with literature, where T2 and T3 are the most prevalent stages at diagnosis.[14,29] In this series they respond for 70.5% of all patients.

Lymphatic invasion in rectal cancer is also very important as prognostic indicators. Positive lymph nodes patients are 3 times greater risk of disease-related death.[3] A Korean study some years ago showed that even in T1 and T2 tumors, N positive staging is a predictor of diminished disease-free survival.[21,30] Most of patients in this series were free of lymphatic invasion (68.8%). Concerning differentiation, it is also known that less differentiated cells in rectal cancer are responsible for poorer prognosis, and is also an important independent factor of recurrence, but moderately

differentiated tumors are majority in this (68%) as well as in other series.[3]

A mean follow-up of 34.1 months was necessary to identify recurrence in 22% of all patients, independently of where disease is installed. This number can be taken as high, when compared to other studies, but when we look only at local recurrence, separating from patients with only distant metastasis, this number falls to 13.1% (16 patients out of 122), which is similar to most of literature.[15,18,31,32] When only local recurrence is studied, incidence can vary from 3% to 35%, depending on follow-up, tumor staging and neoadjuvant therapy. In about 50% of all cases, recurrence is exclusively local, and when surgery is the treatment to this condition, up to 20–30% 5-years survival can be achieved, while palliative radiochemoradiation can give an average of 10–17 months of survival.[8,14,15,17,22]

Initial T stage T3 was found in 70% of all recurrences, which is well justified, as deep tumors are more aggressive. N staging was not consonant with literature.[14] We found 70% of surgical specimens were N0, while in other series N1 or N2 staging respond for up to 54% of all the recurrences. This finding is quite annoying, and it may be telling our group to look harder for cancer in lymphatic tissue in mesorectum and mesocolon.

Time between surgery and diagnosis of recurrence was 23.9 months, which is a little shorter than other series, describing up to 31 months.[16] We had one recurrence diagnosis within 5 months, that could be seen as residual disease, rather than local recurrence, but we chose not to make any distinction between residual disease and recurrence, concerning time of diagnosis after first surgery, as the limit between these two concepts are unclear.

From the patients who developed distant metastasis, most were found on the lungs (33.3%), and liver metastasis occurred in 14.8%. This can be explained by the fact that most of the tumors in this series were extra-peritonial, in the vena cava drainage territory, leading to more lung rather than liver metastasis.

Conclusion

This study shows data similar to literature in most aspects studied, like incidence and place of recurrence. However, some numbers can still be strongly stimulating in pursuing a better surgical technique and overall treatment for our patients, chasing a longer disease-free survival rate.

Conflicts of interest

The authors declare no conflicts of interest.

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