Pattern of Rectal Cancer Recurrence Following Potentially Curative Surgical Treatment

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Abstract

Survival in rectal cancer has been related mainly to clinical and pathological staging. Recurrence is 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 June 2003 and July 2021. After applying the exclusion criteria to 305 patients, 166 patients were analyzed. Global recurrence was found in 18.7% of them, while 7.8% have had local recurrence. Recurrences were diagnosed from 5 to 92 months after the surgical procedure, with a median of 32.5 months. Follow-up varied from 6 to 115 months. Recurrence, in literature, is usually between 3 and 35% in 5 years and shows a 5-year survival rate of only 5%. In around 50% of cases, recurrence is local, confined to the pelvis. This study was consonant with the literature in most aspects evaluated, although a high rate of local recurrence remains a challenge in seeking better surgical outcomes.

Keywords

- rectal neoplasm
- recurrence
- neoplasm recurrence
- colorectal surgery

Introduction

Colorectal cancer is the second most common non-melanoma tumor in Brazil. It is estimated that for each year from 2020 to 2022, there will be a risk of ~ 19.64 new cases per 100,000 men and 19.03 per 100,000 women.[1] Rectal carcinoma corresponds to ~ 30% of colorectal neoplasms.[2]

From a global perspective, colorectal cancer is the 3rd most common neoplasm, being the 2nd leading cause of cancer death in 2018. The incidence of colorectal cancer, especially in the rectum, has decreased in patients over 50 years of age but increased in the age group under 50 in developed countries. The overall mortality rate has decreased due to greater access to diagnosis as well as to better pre and postoperative support, as well as better surgical technique, and access to adjuvant treatment.[3]

Survival and disease-free period are related to genetic, molecular, pathological, clinical, and surgical or chemotherapy treatment factors. It is necessary to assess the prognosis, especially the time of diagnosis, patient age, associated comorbidities, tumor location, and carcinoembryonic antigen levels, and the most relevant information regarding prognosis is the result of the surgical specimen evaluation, which allows the identification of the histopathology of the lesion, depth of invasion, lymphatic involvement, and quality of the surgical specimen.[4,5]

Regarding the surgical technique affecting rectal cancer, the standard is total mesorectal excision (TME) by open, laparoscopic, or robotic approach. Concepts such as routine lateral pelvic lymphadenectomy and high ligation of mesenteric vessels are still matters of debate.[2,6]

Local recurrence and distant metastasis are significant issues due to their impact on morbidity and mortality. The

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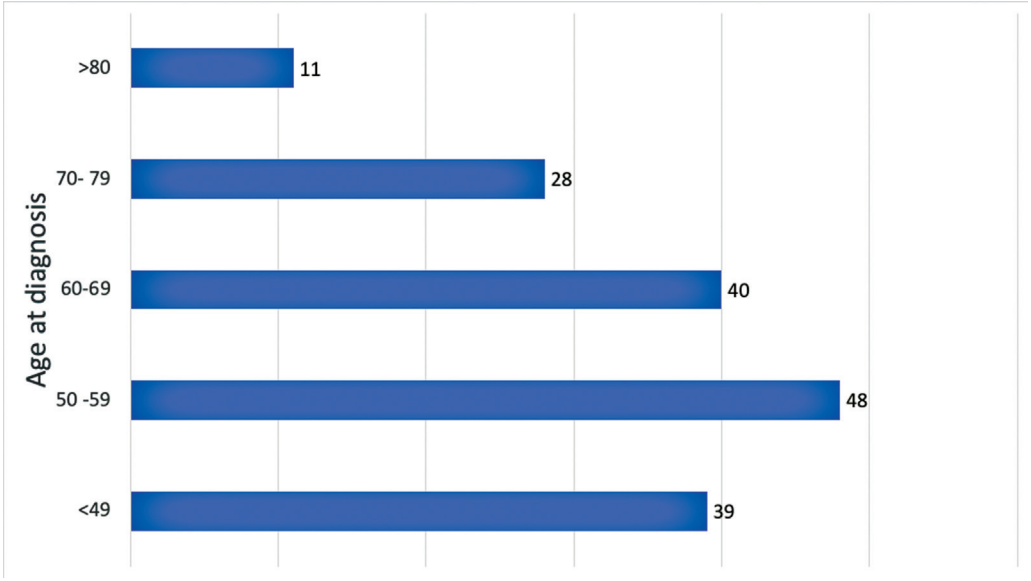

Fig. 1 Age at diagnosis.

local recurrence rate after curative surgery varies between 2.4 and 10%, with the possibility of resection in more than a third of them. Distant metastases arise predominantly in the lung and liver and affect 20 to 50% of patients.[7–9]

With the improvement in staging assessment and more precise indication of neoadjuvant and adjuvant therapy, it has been possible to celebrate a decrease in local recurrence rates and an increase in survival.[7,8,10] Other factors, such as pelvic dissection, adequate surgical margin, complete mesorectal resection, and surgeon experience, should also be considered when evaluating recurrence.[11]

Systematic oncological follow-up with physical examination and imaging tests such as magnetic resonance imaging (MRI) and computed tomography (CT) scans of the abdomen and thorax are important, as they allow early identification of recurrence and new lesions, although they require high investment by the patient and the health system.[8,12]

Purpose

The purpose of the present study is to demonstrate the epidemiology and profile of patients undergoing curative surgery for rectal cancer and to analyze the disease's recurrence rate and pattern.

Methodology

Patient data were obtained from the electronic and physical medical records at Hospital Municipal Dr. Mário Gatti in Campinas, SP, Brazil, covering patients operated by the same surgical team. The ethics committee accepted the request for waiver of informed consent, as it is a retrospective study, and no patient identity could be verified. Initially, 305 patients diagnosed with rectal cancer were identified. The present study included 166 patients who underwent surgery considered to be curative for rectal cancer with at least 6 months of postoperative follow-up. The exclusion criteria were patients who underwent local resection, non-curative surgery with compromised margins, metastasis at diagnosis, follow-up shorter than 6 months, familial polyposis, or incomplete data in their medical records.

The study period consisted of patients admitted from June 2003 to July 2020. The following variables were considered: age at surgery, gender, neoadjuvant therapy, adjuvant therapy, histopathological characteristics, tumor, nodes, and metastases (TNM) classification, type of recurrence, diagnostic method of recurrence, time until recurrence after surgery, and treatment of recurrence. Data are shown in graphs and tables.

Results

Of the group of 166 patients, 75 (45.2%) were women, and 91 (54.8%) were men. Rectal cancer occurred in this group in the age group of 22 to 92 years, with a mean of 59.4 years (►**Fig. 1**).

Total mesorectal excision was performed in 126 patients, with 95 (75.4%) undergoing low anterior resection and 31 (24.6%) abdominoperineal amputation. Total colectomy was performed in 5 (3.1%) patients, and partial mesorectal excision in 35 (21.1%). The choice between open or laparoscopic access was made according to the conditions at the time.

A total of 102 (61.45%) patients underwent neoadjuvant treatment with radiotherapy and chemotherapy, 3 (2.9%) with radiotherapy alone. The total amount of radiotherapy was between 4,500 cGy and 5,040 cGy for 5 weeks. The chemotherapy medication regimen was defined based on the patient's status and drug availability, with one of the following options: fluorouracil starting concurrently with radiotherapy from day 1 to day 5 and from day 20 to day 25; fluorouracil once a week for 5 weeks of radiotherapy, or oral capecitabine during the 5 weeks of radiotherapy. Surgery

Table 1 Tumor, nodes, and metastases staging (7th edition)

T	n	%
T0	18	10.90
Tis	6	3.60
T1	8	4.80
T2	38	22.90
T3	90	54.20
T4	6	3.60
N	**n**	**%**
N0	110	66.30
N1	41	24.70
N2	1	5.9

Table 2 Cancer cell differentiation

Adenocarcinoma	N	%
Moderately differentiated	129	77.71
Poorly differentiated	1	0.60
Well differentiated	17	10.20
Mucinous	1	0.60
Without tumor	18	10.90

was performed from 2.5 weeks to 144 weeks after completion of neoadjuvant therapy.

Classification based on the TNM 7th edition system was used after a histopathological study of the surgical specimen to assess the depth of invasion, lymph node involvement, and distant metastases.

Most tumors were classified as T3 and N0, showing an elevated incidence of advanced disease in the studied group (►**Table 1**). Tumor differentiation of adenocarcinomas was also evaluated, with 129 (77.7%) lesions being moderately differentiated, 17 (10.2%) well-differentiated, and 1 (0.6%) poorly differentiated (►**Table 2**). One patient (0.6%) had a mucinous tumor, and 18 (10.9%) had no tumor in the surgical specimen, demonstrating a complete response to neoadjuvant therapy.

All patients were instructed to return periodically for follow-up after performing the requested exams. The established routine includes digital rectal examination, chest and abdomen CT scans, pelvic MRI, carcinoembryonic antigen (CEA), colonoscopy, and positron-emission tomography (PET-CT), if necessary. The minimum follow-up period was 6 months.

Thirty-one patients (18.7%) had recurrence diagnosed during the follow-up period, and 22 (71%) patients at T3 staging. One patient (3.2%) had recurrence even with T0 staging in the specimen, 7 (22.6%) with T2, and 1 (3.2%) with T4. No patient with stage T1 or Tis had a recurrence. Twenty recurrences (64.5%) were identified in patients without lymph node involvement (N0), while N1 was associated with 10 recurrences (32.3%), and N2 to 1 (3.2%) recurrence (►**Fig. 2**).

Local recurrence was identified in 13 (7.8%) patients, being 7 (4.2%) only local and 6 (3.6%) associated with distant metastases, including hepatic, pulmonary, lymph node, and bone recurrence within this group. Concerning the patients with distant metastasis only, 4 (2.4%) had hepatic involvement, 4 (2.4%) pulmonary, 1 (0.6%) bone and 1 (0.6%) lymph

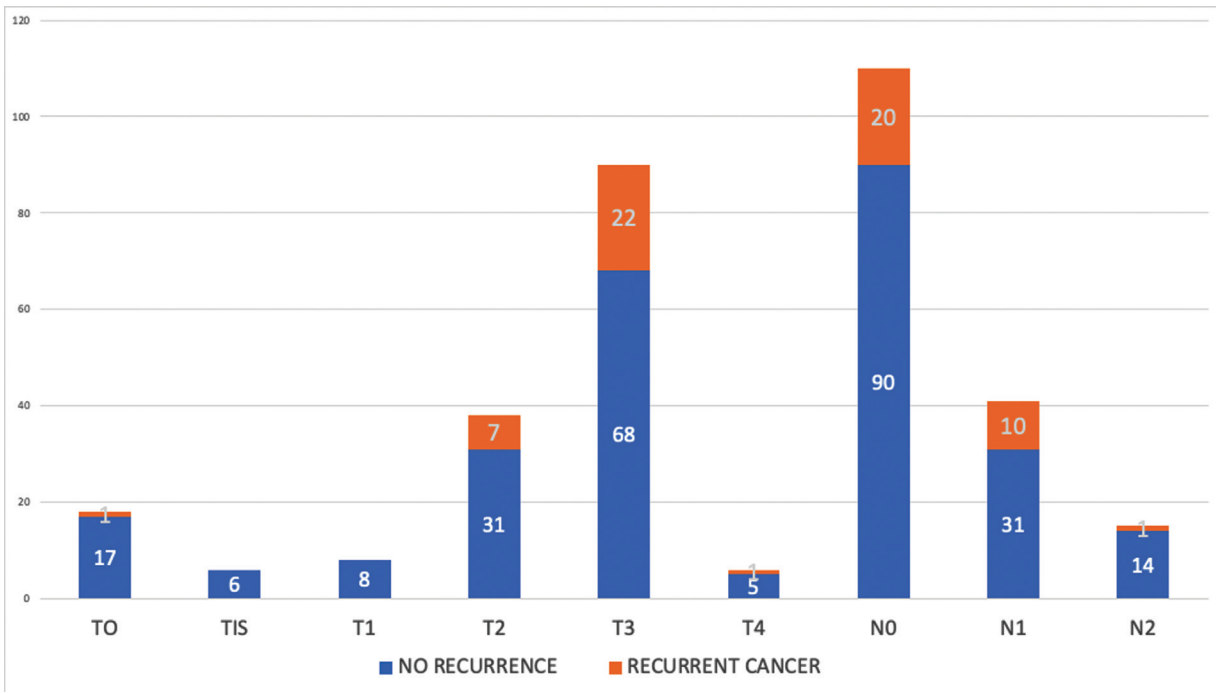

Fig. 2 Recurrence and tumor, nodes, and metastases staging.

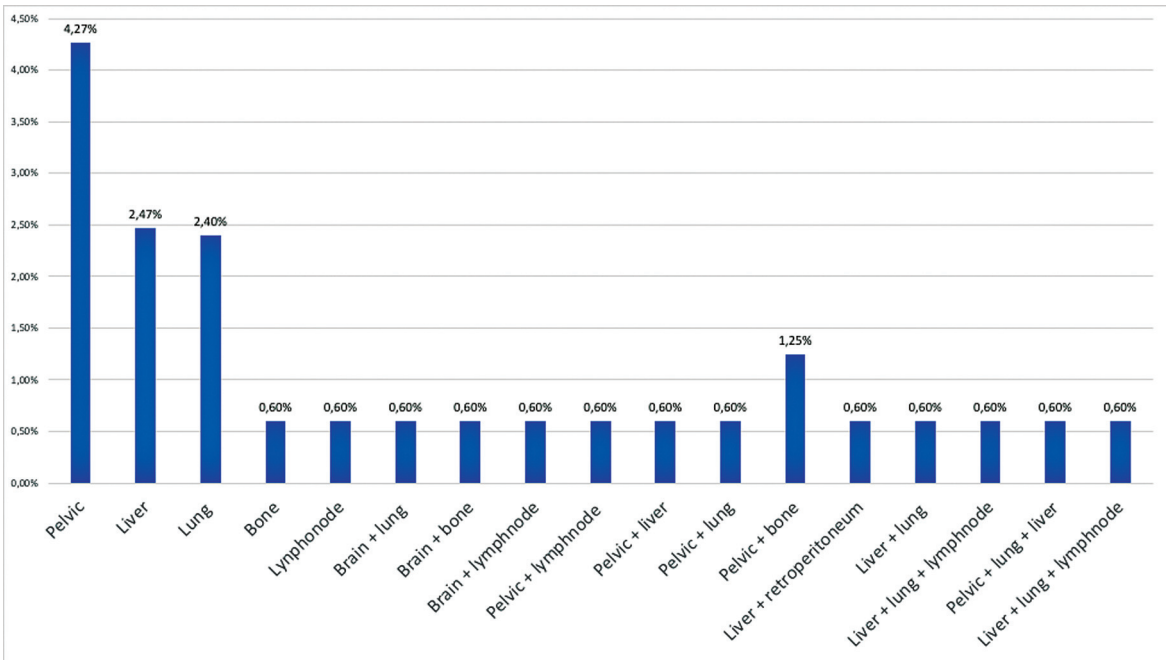

Fig. 3 Site of recurrence.

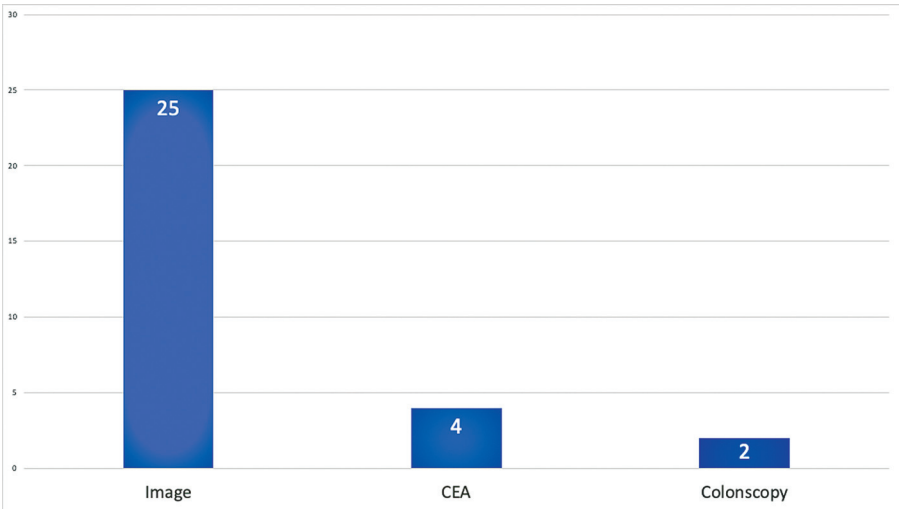

Fig. 4 Diagnosis of recurrence.

node involvement. The other patients presented involvement in more than one distant site differently (►**Fig. 3**).

Recurrences were diagnosed from 5 to 92 months after the surgical procedure. Recurrences in 25 patients (80.7%) were diagnosed with imaging tests, including CT, MRI, and positron emission tomography (PET)-CT, 4 (12.9%) with an elevation of CEA, and 2 (6.4%) with the endoscopic examination (►**Fig. 4**).

The treatment of choice was determined after evaluating the resectability of metastases, the patient's clinical condition, and available therapeutic options. Fourteen patients (45.2%) were submitted to chemotherapy alone, 4 (12.9%) to chemotherapy associated with surgery, and 11 (35.5%) to surgery alone. Two patients had no treatment described in the medical records.

An overview of recurrence pattern is shown in ►**Fig. 5**.

Discussion

Colorectal cancer is a highly prevalent disease, with a continuous need for evolution in its treatment in search of better results. The appropriate surgical technique with total mesorectal resection has been spotlighted as necessary in the short and long-term prognosis, being a fundamental measure concerning the quality of the surgical procedure. Regarding the excellence of adequate treatment, one of the evaluation criteria used is the local or distant recurrence rate.[4,13]

In this study, 166 patients were treated with curative intent, the incidence being higher in men, as predicted by the

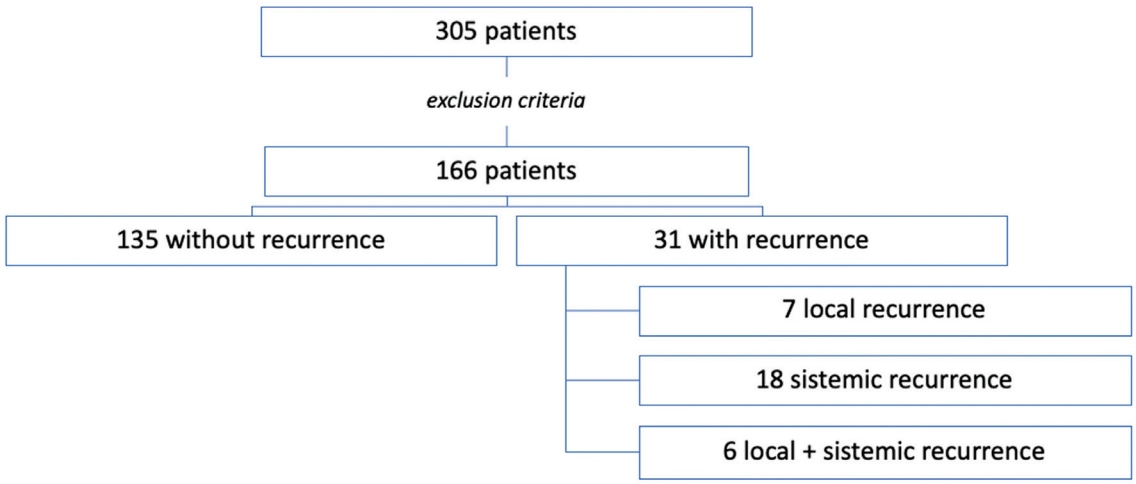

Fig. 5 Design of study.

literature. The mean age at diagnosis, 59.4 years, is consistent with other studies.[1,14] Approximately 23.5% of patients were diagnosed under 50 years of age. This high incidence of neoplasia in young adults is also a trend observed in countries such as the United States, Australia, Canada, and the United Kingdom. It is predicted that by 2030, ~ 23% of rectal tumors will affect patients younger than 50 years, with a more substantial proportional increase in females. The diagnosis of these patients is still challenging since most of them do not have family risk factors or predisposing pathologies, being classified as having a low risk for neoplasia, which favors negligence of symptoms and late diagnosis. The pathophysiology of this increase is still poorly understood, with genetic changes, environments, and lifestyle being taken into account as contributing factors. Because of this tendency, the American Cancer Society recommends starting screening with endoscopic examination from 45 years.[1,15]

The treatment of colorectal neoplasia must involve a multidisciplinary team composed of a surgeon, oncologist, pathologist, radiotherapist, nursing, and support from other professionals involved. Due to the plurality of existing protocols, most services evaluate and adopt standard protocols according to available resources. The patients in this study were treated without a well-established and integrated multidisciplinary team, so it is possible to notice the wide assortment of protocols used with different medications and radiation doses in their treatments.[16]

The broad time interval of 2.5 to 144 weeks from the end of neoadjuvant therapy to the time of surgery occurs as some patients had a complete clinical response to neoadjuvant therapy with subsequent lesion growth and the demand for surgery. According to the ESMO guideline, a complete clinical response can be observed in an average of 10 to 40% of patients after 12 weeks from treatment.[12] In pioneering studies, Habr-Gama and colleagues reported a complete clinical response in 26 to 38% of patients.[12,17] The response to neoadjuvant treatment in the services in question was evaluated after 8 to 12 weeks of completion of treatment. A complete response criterion includes the identification of fibrosis at MRI of the tumor site, a good quality endoscopic examination with no sign of tumor with only scar tissue, and digital rectal examination without lesion. Patients who met all the criteria were subjected to strict follow-up control, performing MRI, digital and endoscopic examination every 3 to 4 months, with surgery being indicated in the appearance of a suspicious lesion. Patients who had lesions found in exams performed 8 to 12 weeks after neoadjuvant therapy had surgery immediately indicated.[12,18]

The most performed primary surgery was low anterior resection (75.4%), with abdominoperineal amputation of the rectum being less frequent, consistent with the literature. With a curative proposal, new operative techniques, equipment, and neoadjuvant therapy protocols have allowed for less aggressive surgeries.[19]

Stages T3 to T4 tumors have a higher death risk when compared with T1 to T2, and the depth of invasion is correlated with the prognosis. The literature shows that the most recurrent stages of diagnosis are T2 and T3, which were also identified in this study, in which most patients (54.2%) were diagnosed with stage T3 disease.[20–22] Lymphatic invasion is also essential in assessing the prognosis since patients with positive lymph nodes are 3 times more likely to have disease-related death.[22,23] Most patients in this series (66.3%) did not present lymph node involvement, with only 7% classified as N1 and 9% as N2. Regarding cell differentiation, in this series, a predominance of moderately differentiated tumors was observed, corresponding to 77.7% of the patients, which is consistent with the literature. It is important to emphasize that the less differentiated the tumor cells, the worse the prognosis.[23] In more advanced stages of the disease, it becomes necessary to evaluate new strategies to enable earlier diagnosis and better treatment results.[24]

There are multiple postoperative oncological follow-up protocols, and there is no consensus on the ideal frequency of examinations.[12] After being discharged, the patients returned in 7 to 10 days for postoperative medical evaluation and, after that, to assess anatomopathological results and determine whether to refer for adjuvant therapy. The

patients' follow-up for the first 2 years was performed every 6 months, with CT of the chest, abdomen, and MRI of the pelvis, with an endoscopic examination being performed in the 1st year. From the 2nd year onwards, the exams were performed annually; from the 5th year onwards, every 2 years until completing 10 years of follow-up, with subsequent outpatient discharge. During follow-up, PET CT was performed to investigate distant metastases and local recurrence if there was an increase in carcinoembryonic antigen (CEA) or a suspicious image in CT or MRI. In the context of the follow-up protocol adopted by the service, 80.7% of recurrences were identified by imaging tests, which, through technological advances, are increasingly sensitive and specific, allowing for a more precise diagnosis of local and distant tumor recurrence.[25]

The overall recurrence rate was 18.67%, with 7.8% of local recurrence with or without metastasis, consistent with the literature that assumes a rate of 2.4 to 10%. Regarding distant recurrence, associated or not, it was identified in 24 (14.45%) patients with a predominance of hepatic and pulmonary involvement, as described in the literature. Twelve patients, which corresponds to 38.7% of patients with recurrence, had pulmonary involvement, which can be explained by the more significant amount of extraperitoneal tumor with drainage to the vena cava, leading to greater pulmonary involvement than hepatic involvement.[7,8,12]

Adequate histopathological evaluation of the surgical specimen is essential for determining adjuvant therapy and the subsequent treatment steps. In 71% of the identified recurrences, the patients were on stage T3. This proportion is consistent with the literature since the deeper the tumor invasion, the greater the risk of local and systemic recurrence. For the staging process to be considered proper, it is recommended that at least 12 lymph nodes in the surgical specimen are evaluated.[10] A proportion of 64.5% of recurrences was identified in N0 patients. This rate is not compatible with the literature, according to which $\sim$ 54% of recurrences are identified in patients N1 or N2.[20] Such discrepancy, thus, suggests a possible inadequate histopathological evaluation of the surgical specimens in the services in question.[12]

The interval between surgery and the diagnosis of recurrence ranged from 5 to 92 months, with a mean of 32.46 months, which is consistent with the literature.[22] One patient was diagnosed with recurrence 5 months after the surgery, which can be interpreted as a residual disease. However, we chose to consider it a recurrence since there is no explicit limit regarding the time interval between residual or recurrent disease.

The treatment of local or distant recurrence should be evaluated by a multidisciplinary and individualized group, considering all therapeutic possibilities and the patient's clinical condition. Most of the patients in the study (45.2%) underwent chemotherapy alone due to the significant number of findings of more than one metastasis site. In surgical cases, surgical excision with complete resection of the recurrence with free margins is still the gold-standard treatment with the best prognosis. In the present study, it was the therapeutic choice in 35.5% of patients.[26]

This study shows data similar to those of the literature in most respects, such as incidence of local recurrence and the site of distant recurrence. However, some results serve as a stimulus for the search for improvement in surgical and drug treatment to increase patients' disease-free survival.

Author's Contribution

Gustavo Sevá-Pereira and Vitória Souza Oliveira were responsible for conception and design and wrote the main manuscript text.

Paula Buozzi Tarabay and Gabriela Domingues Andrade Ribeiro reviewed the data analisys.

Joaquim José de Oliveira Filho helped with data collection and critically reviewed the manuscript.

Marcello Imbrizzi Rabello helped with the writing correction and critically reviewed the manuscript.

Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author, G. S. P. The data are not publicly available due to ethical and privacy restrictions.

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Conflict of Interests

The authors have no conflict of interests to declare.

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