Prognostic analysis for carcinoid tumors of the rectum: a single institutional analysis of 106 cases

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Abstract:

Aim: Rectal carcinoids is a rare rectal tumor with a good prognosis. The aim of this study was to assess its clinicopathological characteristics and prognostic factors in a single institution.

Method: Clinical and pathological information was retrospectively collected in a single institution and patients' outcomes were determined. Multivariate analyses were performed to find independent prognostic factors attributed to overall survival.

Results: 106 patients with rectal carcinoid were included. (66%) underwent trananal local excision and (34%) had transabdominal surgery. The 5 year survival rate wass 87%. Muscularis invasion was the only independent prognostic factor for predicting 5 year survival (p=0.00046). Tumor size was found significantly to be associated with muscular invasion (p=0.00003). The area under the curve (AUC) of tumor size in the (ROC) curve for predicting muscular invasion was 0.92.

Conclusion: Patients with rectal carcinoid have a good prognosis. Muscular invasion is an independent risk factor of survival.

Introduction:

Carcinoid tumor is rare, comprising nearly 0.49% of all malignancies[1]. Most arise in the gastrointestinal tract, predominantly in the small bowel[2]. In the large bowel the rectum is the most frequently involved location[3]. Rectal carcinoid appears to have increased in incidence over the past 30 years this may be due in part to improvements in diagnostic technology, such as endoscopy, but increased awareness may be a factor. In a series of 13,715 patients with carcinoid tumors, rectal carcinoids were the third most frequent at 13.7% gastrointestinal. Most rectal carcinoids are localized at the time of diagnosis and a have low propensity for metastasis[4]. It is usually considered a less aggressive disease with reported five year survival rates of over 85% for all stages of patients in most studies. However, nearly 4 to 18% of patients still developed metastatic disease [1, 2].

Rectal carcinoids have been limited by local excision or tranabdominal resection. Criteria for selection of treatment are related to prognosis. Muscular invasion and tumor diameter are the most widely considered risk factors.

We report a retrospective study to assess the clinicopathological characteristics and prognostic factors of rectal carcinoid in a single institution over 21 years.

Method:

Between 1985 and 2006, 106 patients with rectal carcinoid, located within 15cm from the anal verge were treated in the Department of Surgery, Cancer Hospital of Fudan University. Demographic and pathological features were retrospectively accessed from the institutional colorectal database.

The diagnosis of rectal carcinoid was confirmed in all cases by an independent pathologist without knowledge of clinical details. Carcinoid tumors were defined as having one or more typical morphologic patterns characteristic of well-differentiated endocrine neoplasms with uniform nuclei having coarsely clumped chromatin. All cases in our series were pathologically confirmed as well differentiated endocrine neoplasms according to the World Health Organization classification scheme for neuroendocrine tumors[5]. The presence of neuroendocrine differentiation is evidenced by positive immunohistochemical staining for chromogranin or synaptophysin. Importantly, the mitotic rate consistently less than 10 mitoses per 10 high-power fields (HPF) (or 50/50 HPF) and neuroendocrine neoplasms with a higher mitotic rate are regarded as high grade neuroendocrine carcinomas.

The size of the primary lesion is given by the largest tumor diameter measured after fixation of the specimens and recorded in the original pathological report. The degree of muscular invasion is also evaluated histopathologically and is defined as (T2) (tumor invading the muscularis propria), (T3) (tumour penetrating the muscularis propria) and T4 where the visceral peritoneum is directly invaded or the tumour is directly invading other structures. Invasion of the submucosa (T1) is classified as non-muscular invasion. A clear margin was assessed by histopathological examination

Surgical Technique

All patients underwent transanal local excision or transabdominal surgery, including anterior resection, abdominal perineal resection, Hartmann's procedure, or a pull-through technique. Palliative operations performed for patients with metastatic disease included biopsy, colostomy and palliative resection of the primary lesions.

Follow-up

All patients were followed up at 3 to 6 months after surgery during the first 3 years and annually thereafter. Digital examination, Chest X ray, abdomino-pelvic ultrasound or CT scan were used. Recurrence was defined as local or distant disease diagnosed more than three months after the initial surgery. All surviving patients were followed over a medium follow-up of 67 months. Three patients were lost to follow up leaving 103 who were included in the present study.

Statistical Analysis

The Chi-square test and t test was used for the analysis of categorial and continuous variables, comparing the differences of clinical features between patients treated by the two techniques. Five and 10-year survival were analysed by the Kaplan-Meier methodology. Univariate and multivariate Cox regression was used to assess potential factors of outcome. Logistic regression was used to evaluate the value of tumor size in predicting muscular invasion. The Receiver Operator Characteristics (ROC) curve was drawn and the area under the curve (AUC) was computed to assess the accuracy of prediction. A P value of < 0.05 was considered to be statistically significant.

Results:

Of the 106 patients, 70 (66%) were treated by trananal local excision and 36 (34%) by transabdominal surgery. Of the 14 patients with a tumor size of more than 20 mm, five underwent local excision. Of the 92 with turmor size of less than 20 mm, 66 underwent local excision. None of the patients had carcinoid syndrome. Eleven (10.4%) patients had synchronous metastatic disease. Seven (6.6%) underwent postoperative chemoradiotherapy, and 10 (9.4%) had postoperative chemotherapy with various chemotherapeutic regimens. Multiple lesions were observed in 11(10.4%) patients, of whom 6 (5.7%) had multiple carcinoids, and 5 (4.7%) a metachronous non-carcinoid malignancy. The clinicopathological features are listed in Table 1.

In the 103 patients with available follow up, 14 (13.6%) had died of whom 13 (12.6%) had died of carcinoid. The overall 5 year survival rate was 87.0%. For the 92 patients without synchronous distant metastasis, the overall 5-year survival rate was 93.6%. For the 11 patients with synchronous distant metastasis, the medium survival time was 16 months.

Univariate Cox regression analysis showed muscular invasion and tumor size to be significantly associated with the overall 5 year survival. Muscular invasion was, however, the only independent prognostic factor for predicting overall 5-year survival (hazard ratio 38.0 (95% CI : 4.9-290.5; p=0.00046). Kaplan-Meier analysis showed that the 5 and 10 year survival rates for patients without muscular invasion were 100% and 95%, sigificantly higher than in patients with muscularis invasion (5 and 10 year survival rates 56.7%, p=0.00001) (Fig 1).

Although tumor diameter was not found significantly to be associated with survival (p=0.15), we further analyzed the relationship between tumor size and the status of muscular invasion. For the 31 patients with muscular invasion, the mean tumor size was 32 mm (range 4 to 80 mm); and for the 75 patients without muscular invasion, it was 8 mm (range 2 to 30 mm). Logistic regression also showed that tumor diameter was the only significant predictor of muscular invasion (odds ratio of 12.6 (95% CI: 5.5-29,P=0.0003). The area under the ROC curve of tumor size for predicting muscular invasion was 0.92 (95% CI: 0.85-0.99). When 15 mm were chosen as the cut-off, the

sensitivity and specificity of predicting muscularis invasion were 80.6% and 89.3%, and when 20 mm were chosen these were 74.2% and 97.3%.

Discussion:

In this study of 106 rectal carcinoid tumors those with larger diameter, muscular invasion and distant metastasis were more likely to undergo transabdominal surgery. The incidence of 10.4% synchronous metastatic disease is in line with the 4 to 18% of patients reported in other series [2, 6, 7]. In a population-based review of carcinoid tumors, Maggard et al. found 6.8% to have synchronous distant metastases out of 1217 patients with rectal carcinoid [2]. Fahy et al. also reported 17.5% in a series of 70 patients [6].

Rectal carcinoid tumors occur in 2% to 4.5% of patients with intestinal carcinoid tumors [8]. Patients with carcinoid have , however, a higher risk for synchronous and metachronous nonendocrine malignancies[9]. The rate of a second primary malignancy with a carcinoid tumor ranges from 12 to 46%, (average 17 %). This is significant when compared with the rates of second primary malignancy in other cancers such as adenocarcinoma of the gastrointestinal or genitourinary systems[10, 11]. In the present series, there were six (5.7%) patients with a synchronous multiple carcinoid tumor and five (4.7%) with simultaneous other malignancies.

Patients with a carcinoid tumor of the rectum generally survive longer than than those with carcinoids in other sites of the gastrointestinal tract. In a series of 13,715, patients with carcinoid included in the surveillance, epidemiology, and end results (SEER) program from 1973 to 1999 and in two earlier NCI projects, 5 year survival rates were 75.2% between 1973 and 1991 and 88.3% from 1992 to 1999 [1]. An updated analysis by Maggard et al. including 11,427 carcinoids of SEER data also reported a 5 year survival rate of 87.5% for all stage rectal carcinoids [2]. Soga reported 85.4% of 5 year survival rate for rectal carcinoids out of a series of 10,804 carcinoids from the Niigate Registry derived from 64 countries[12]. These authors performed a pooled analysis of 1271 cases from 465 articles published from 1912, and found a high rate of 5 year survival rate[13]. In a series of 1914 gastrointestinal carcinoids, the same authors also reported a 5 year survival rate of 88.1% for 822 patients with rectal carcinoids [14]. Although 10.4% of patients had synchronous distant metastases, the overall 5-year survival rate in this study was 87%, which is comparable to other reported series. It is not possible from the available data to determine the impact of chemotherapy in this disease.

Most of the controversies of the treatment of rectal carcinoid focus on patient selection for more aggressive surgical treatment, such as anterior resection or abdominoperineal resection. Most large studies are population-based and include carcinoids of the whole body, with rectal carcinoid being small part of the whole. Thus it is not possible to obtain detailed clinicopathological and prognostic factors from these. There have only been a few studies on the prognosis of rectal

carcinoid and the number of cases in most studies is less than a hundred. Preoperative collectable data or information obtained from local excision are valuable for selecting patients for more aggressive surgery [15]. In the present study of over 100 rectal carcinoid tumors, the degree of invasion of the muscular progeria was found to be the only independent risk factor predicting overall survival. This has been shown in other studies[16-18]. Thus Mani et al. reviewed more than 200 reports of rectal carcinoid and stated muscular invasion and tumour size were the two most important prognostic factors[19]. There was less consensus on the latter, however, in a study of 70 rectal carcinoids which categorized tumor size into three groups (<10 mm, 10-19 mm, $\geq$20 mm). An association with 5 year disease free survival on the univariate analysis was the only correlation found [6]. Mani et al. report, the incidence of metastatic disease for tumors <10 mm, 10-19 mm and $\geq$20 mm to be <2%, 10-15% and 60-80%, respectively[19]. In another series of 777 rectal carcinoids, however, Soga et al. also reported higher metastastatic rates for different size of tumor, being 9.7%, 27.6% and 56.7% for tumors size of <10 mm, 10-19 mm and $\geq$20 mm, respectively[14]. Sauven et al. also found tumors greater than 20 mm had a worse prognosis than those less than 20 mm. These authors also found the degree of muscular invasion increased for tumours of <10 mm, 10-19 mm, and $\geq$20 mm in diameter[17]. In a report of 97 gastrointestinal carcinoid tumors, there was no relationship between tumor size and 5 year disease free survival[16]. In another series of 154 patients with gastrointestinal carcinoid, the tumor size was also not related to prognosis[18]. The tumor size in the present study was not found to be significantly associated with outcome in the multivariate analysis when musclar invasion was included, but further analysis found that tumor size was a significant factor for predicting muscular invasion. The interaction between size and depth of invasion was reported to be important when predicting the behavior of rectal carcinoids[20]. Specifically when a size of 15 mm was chosen as a cut off, the sensitivity and specificity of predicting muscularis invasion were 80.6% and 89.3% and when a size of 20 mm was chosen these were 74.2% and 97.3%. When the morbidity of rectal surgery is taken into account, our results suggest a more selective choice of operation. Patients can be justifiably treated by an anal sphincter preservation operation, when a diameter of 15 mm is used to select local excision or transabdominal excision. Where the tumor is located so distally that sphincter preservation is not feasible, a diameter of 20 mm may be an appropriate limit for local excision.

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Table 1. The clinicopathological characteristics of rectal carcinoids treated by different types of surgery

Characteristics		Transanal Local Excision (n=70)	Transabdominal Surgery (n=36)	p-value
Sex	Male	32 (30.2%)	24 (22.7%)	0.04
	Female	38 (35.8%)	12 (11.3%)	
Age (Mean±SD, years)		50±14	48±11	0.40
Penetration	Present	9 (8.5%)	22 (20.8%)	2.0×10^{-7}
	Absent	61 (57.5%)	14 (13.2%)	
Tumor diameter (Mean±SD, cm)		0.85±0.52	2.8±1.9	1.0×10^{-7}
Synchronous Metastasis		1 (1.4%)	10 (27.7%)	2.0×10^{-5}

Table 2. Univariate analysis of factors predicting 5 year survival

Variables	HR	95% CI	
Sex Male/Female	1.30	0.45-3.77	0.63
Age	1.04	0.99-1.09	0.06
Muscular invasion	37.9	5.0-290	0.0005
Tumor diameter	1.58	1.31-1.91	2.0×10^{-6}

Figure 1 Life table analysis of survival related to penetration or non-penetration of the muscularis propria