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ORIGINAL ARTICLE

Malignancies of the anal canal: A multi-center retrospective analysis in South China Population

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Summary

Purpose: *Malignancies of the anal canal are rare diseases associated with limited reports and insufficient data. The purpose of this study was to evaluate the spectrum of pathological subtypes, therapeutic modalities and prognosis of patients in the Chinese population with anal canal malignancies.*

Methods: *A retrospective consecutive series of patients with malignancies of the anal canal at 4 institutions in China between January 1990 and December 2011 was studied. The patient demographic data, including age, gender, tumor stage, initial symptoms, pathological diagnosis, treatment and survival, were collected and analyzed from the hospitals' databases.*

Results: *A total of 180 patients (90 males, 90 females) with anal canal malignancies was identified. Their median age was 58 years (range 17–88). The 3 most common pathological subtypes were adenocarcinoma (N=129, 71.7%), squamous cell carcinoma (SCC; N=21, 11.7%) and melanoma (N=15, 8.3%). Ninety-five adenocarcinoma patients and 10 SCC patients were managed with abdominoperineal resection (APR). With a median follow-up time of 28.9 months (range 1–173), the 5-year overall survival (OS) rates for all patients, adenocarcinoma patients, SCC patients and melanoma patients were 41.9, 40.6, 44.5 and 14.8% respectively, and the median OS time were 46.8, 50.1, 52.5 and 25.0 months, respectively (p=0.173).*

Conclusion: *Adenocarcinoma was the major histological subtype in Chinese patients with anal canal malignancies. APR-based combined modality treatment was the first choice for the past two decades, whereas multidisciplinary treatment was not performed adequately. The management of SCC must be standardized in South China population. In the future, randomized clinical trials are warranted for the optimal treatment options of anal canal adenocarcinoma patients.*

Key words: *adenocarcinoma, anal canal, malignancy, South China, squamous cell carcinoma*

Introduction

Anal canal cancer is extremely rare, accounting for approximately 1% of all digestive tract cancers [1-3]. Owing to its low incidence of compared with colorectal cancer, reports regarding anal canal malignancies have been insufficient over the last several decades.

Malignancies occurring in the anal canal could be categorized into several histological subtypes, including SCC, adenocarcinoma, melanoma and other types such as lymphoma. The incidence of each type varies significantly among different populations [4-6]. In Western countries, epidermoid carcinoma is the most frequent subtype, comprising 80–90% of all cases [1, 2, 7-11].

However, the epidemiology, etiology, treatment strategy and prognosis are different in Asian patients. There are few published reports [5,6] that have reviewed Asian patients with anal canal malignancies, and all of these studies described a small, single-institute series of cases. Hence, the purpose of our study was to identify the spectrum of pathological types and analyze the therapeu-

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tic modalities and prognosis of patients with anal canal malignancies. We also tried to elucidate the current status of treatment in China and provide useful information to guide treatment strategies in the future.

Methods

Definition of anal canal malignancies

There are several different definitions of the anal canal, such as anatomical, surgical, oncological, embryological and histological. The tumors occurring from below the anorectal ring (anorectal junction) to the anal verge were considered anal canal malignancies according to the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC) as previously defined [7], as well as the surgical concept of the anal canal. Because the average length of the anal canal is 4 to 5 cm [2,7,8,12,13], our current study enrolled patients with tumors located in the proximal part of the intestinal tract within a 5-cm distance from the anal verge.

Patients

We retrospectively reviewed 180 patients (90 female and 90 male, median age at diagnosis 58 years, range 17-88) with anal canal malignancies who were treated at 4 institutions, including Sun Yat-Sen University Cancer Center, the First Affiliated Hospital of Sun Yat-Sen University, Sun Yat-Sen Memorial Hospital and the First People's Hospital of Foshan City from January 1990 to December 2011. The patient records were collected and analyzed from the hospitals' databases and the factors studied were age, gender, tumor stage, initial symptoms, pathological diagnosis, treatment and survival. All of the tumors were confirmed by histopathology. Low rectal tumors extending distally into the anal canal were excluded.

Statistics

All the data were analyzed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). The related clinical factors were appropriately described, such as presenting symptoms and proportion of each pathological subtype. OS was defined as the time from the date of diagnosis to the date of death or the last known follow-up visit. The Kaplan–Meier method was used to calculate OS, and log-rank analysis was used for comparison between groups with different pathological subtypes. A p value less than 0.05 was considered to be statistically significant.

Results

Pathological type and clinical presentation

One hundred twenty-nine (71.7%) patients had histologically confirmed adenocarcinoma. The other pathological subtypes were SCC in 21 patients (11.7%), melanoma in 15 (8.3%), undifferentiated carcinoma in 9 (5.0%), gastrointestinal stromal tumors (GIST) in 3 (1.7%), neuroendocrine tumors (NETs) in 2 (1.1%) and lymphoma in 1 (0.6%) patient. The most common symptoms at presentation were bleeding (74.4%), diarrhea (39.4%), tenesmus (32.8%), pain (30.6%) and weight loss (30.6%). A less common symptom was tapering of the stool (22.8%). Clinical findings included presence of a perianal mass (15.5%) and inguinal adenopathy (14.4%). Of the total cohort, 21 patients (11.7%) were positive for hepatitis B vitus (HBV) infection. Thirty-nine patients had cigarette addiction, and most of the tobacco-addicted patients were male (Table 1).

Treatment modalities
Adenocarcinoma/Squamous cell carcinoma

Among the 150 patients with the two most common pathological types (adenocarcinoma/SCC, N=129/21), 105 (adenocarcinoma/SCC, N=95/10, 70%) underwent radical APR, and 45 (adenocarcinoma/SCC, N=30/11, 30%) did not undergo APR. Among the 105 patients with APR therapy, 35 (adenocarcinoma/SCC, N=31/4, 23.3%) were not administered neoadjuvant/adjuvant treatment. Nine patients (adenocarcinoma/SCC, N=8/1, 6.0%) underwent adjuvant radiation therapy, whereas 13 patients (adenocarcinoma/SCC, N=11/2, 8.7%) underwent adjuvant chemoradiation (CRT), and 45 patients (adenocarcinoma/SCC, N=43/2, 30%) underwent adjuvant chemotherapy. The regimens most frequently administered as adjuvant chemotherapy to patients with adecarcinoma were FOLFOX (N=26) and 5-FU/CF (N=14) with 4 median number of courses. The regimens used for SCC patients varied significantly from a fluorouracil-based combination to cisplatin- and paclitaxel-containing regimens. Only 2 patients (adenocarcinoma/SCC, N=1/1, 1.3%) received neoadjuvant radiation, and one adenocarcinoma patient (0.7%) received neoadjuvant concurrent CRT before radical APR.

Among the non-APR patient group (N=45), 24 patients (adenocarcinoma/SCC, N=21/3, 16%) underwent palliative surgery. Six patients (adenocarcinoma/SCC, N=5/1) underwent postoperative chemotherapy, and 6 (adenocarcinoma/SCC, N=5/1) underwent postoperative radiation. Four (2.7%) SCC patients were administered first-line palliative chemotherapy alone. Five patients (adenocarcinoma/SCC, N=3/2, 3.3%) underwent first-

Table 1. Patient and tumor characteristics

Characteristics	*N*	*%*
Gender		
Male	90	50
Female	90	50
Age, years		
Median	58	
Range	17-88	
HbsAg status		
Positive	21	11.7
Negative	133	72.9
Unknown	26	11.4
Smoking status		
No	141	78.3
Yes	39	21.7
Pathological subtype		
Adenocarcinoma	129	71.7
Squamous cell carcinoma	21	11.7
Melanoma	15	8.3
Lymphoma	1	0.6
GIST	3	1.7
NET	2	1.1
Undifferentiated carcinoma	9	5.0
Initial symptoms/findings		
Bleeding	134	74.4
Diarrhea	71	39.4
Pain	55	30.6
Perianal mass	27	15.0
Tenesmus	59	32.8
Inguinal adenopathy	26	14.4
Thinned stool	41	22.8
Weight loss	55	30.6

GIST: gastrointestinal stromal tumors, NET: neutroendocrine tumors

line definitive concurrent CRT, while one (0.7%) adenocarcinoma patient underwent initial radiation therapy alone. The remaining 11 patients (adenocarcinoma/SCC, N=9/2, 7.3%) received no treatment.

Melanoma

Among the 15 anal canal melanoma patients, 11 underwent APR and 2 local tumor excision. The remaining 2 melanoma patients underwent palliative chemotherapy: one patient was administered single-agent dacarbazine and the other one a combination of dacarbazine, vindesine and cisplatin.

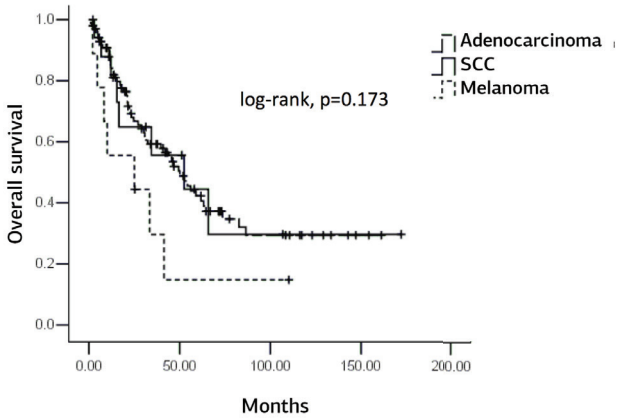

Figure 1. Overall survival according to various pathological subtypes.

Lymphoma

The patient with primary anal canal non-Hodgkin's lymphoma received 4 cycles of CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine and prednisone) with complete remission.

GIST and NETs

Three patients with GIST underwent APR and were administered imatinib as postoperative adjuvant therapy; 2 of them were doing well on follow-up. The 2 patients with NET died of disease progression. The exact tumor grade for the NETs was unclear.

Detailed tumor stage and grade distribution and treatments performed are summarized in Table 2.

Outcome

One hundred thirty-four patients were successfully followed up. The median duration of follow-up was 28.9 months (range 1–173). The 3- and 5-year OS were 55.4 and 41.9%, respectively, for the entire study group. We further analysed the survival data according to the different pathological subtypes. The 3-year OS for adenocarcinoma, SCC and melanoma were 57.8, 55.6 and 29.6% (p=0.173), respectively, whereas the 5-year OS for adenocarcinoma, SCC and melanoma was 40.6, 44.5 and 14.8% (p=0.173), respectively. The estimated median OS of the entire study group was 46.8% months, and for adenocarcinoma, SCC and melanoma it was 50.1, 52.5 and 25.0 months (p=0.173), respectively. An obviously inferior survival was observed in melanoma patients compared with that of adenocarcinoma and SCC patients, although without statistical significance (log-rank, p=0.173; Figure 1 and Table 3).

Table 2. Tumor stage, grade distribution and treatments performed

	All protocol patients (N=180)	*Patients with adenocarcinoma (N=129)*	*Patients with SCC (N=21)*
Stage			
I		7	0
II		36	4
III		49	9
IV		11	2
Unknown		26	6
Grade			
I		20	3
II		72	9
III		13	3
ND		24	6
Surgery			
APR	122	95	10
Other	32	20	6
No surgery	26	14	5
Chemotherapy			
Total	87	71	9
Adjuvant	75	64	4
No chemotherapy	93	58	12
Radiation			
Total	47	38	6
Adjuvant	10	8	1
First line CCRT	5	3	2
Neoadjuvant CRT/RT	3	2	1
No radiotherapy	133	91	15

ND: not done, APR: abdominoperineal resection, CCRT: concurrent chemoradiation, CRT: chemoradiation, RT: radiation therapy, SCC: squamous cell carcinoma

Table 3. Three- and 5-year overall survival

Subtype	*3-year OS %*	*5-year OS %*	*Median OS (months) (95% CI)*
All patients	55.4	41.9	46.8 (31.3-62.3)
Adenocarcinoma	57.8	40.6	50.1 (37.7-62.4)
SCC	55.6	44.5	52.5 (4.8-101.1)
Melanoma	29.6	14.8	25.0 (0-68.0)

p=0.173. SCC: squamous cell carcinoma, OS: overall survival

Discussion

Malignancies occurring in the anal canal are extremely rare [7,12], whereas various tumor types can develop in this region, reflecting its complexity in anatomy and histology. Our study is superior compared to other similar studies in terms of sample size and it is the first multi-center retrospective study focusing on anal canal malignancies in an Asian population.

The distribution of pathological subtypes seemed to vary among different populations. In Western countries, the most frequent histological subtype for anal canal malignancies is SCC [1]. However, Eastern countries possess a distinct histological spectrum with a relatively higher proportion of anal canal adenocarcinoma in contrast to Western countries. In our study, 129 (70%) patients had adenocarcinoma, a finding that was consistent with previous reports in Asian populations [4,6], while the incidence of SCC was quite low (11.7%).

Human immunodeficiency virus (HIV) and human papillomavirus (HPV) infections are well-known risk factors for SCC of the anal canal [2,7,10,13]. These sexual transmission-related factors increased the risk of SCC, contributing particularly to the high incidence of SCC in Western countries vs Eastern countries [14]. Unfortunately, we failed to collect sufficient data for HPV and HIV infection to identify the exact incidence. However, we assessed the HBV infection rate of our patients which was similar to the average infection rate in the general Chinese population, failing to demonstrate a relationship between HBV infection and anal canal cancer.

The lack of specific symptoms at presentation is a critical reason for misdiagnosis and delayed treatment. In the present study the most common symptoms of anal canal malignancy were nonspecific [10], and included bleeding, diarrhea, tenesmus and pain. Careful physical examination, including digital rectal examination and superficial lymph node palpation, could provide valuable information [15].

The standard management of SCC of the anal canal has been well established in Western countries. Before the 1980s, radical surgery with APR was the most frequently recommended treatment. In 1974, Nigro et al. [16] were the first to introduce preoperative concomitant CRT for anal cancer and found the majority of the resected specimens pathologically tumor-free. So, it soon became doubtful whether radical surgery was necessary. Subsequently, 3 important randomized clinical trials [17-19] established CRT as the gold standard of care for locoregional anal canal epidermoid cancer, whereas surgery remained as salvage treatment for local occurrence [12].

Unfortunately, in the past several decades, some Chinese doctors were unfamiliar with this treatment principal due to the rarity of the anal SCC and lacked radiation equipment in some general hospitals. In our cohort, most of the patients (N=16) underwent initial surgery, while only 2 patients underwent definitive concurrent CRT. Thus, 3- and 5-year OS rates were 55.6% and 44.5%, respectively, for our SCC patients, a finding that was clearly unfavorable compared with data reported by Western authors [20]. Moreover, APR caused irreversible organ dysfunction like fecal incontinence, and a poor quality of life. Considering the points mentioned above, to prolong survival and improve quality of life, it is urgent to standardize and popularize treatment principles of anal canal SCC patients in China.

Adenocarcinoma represented the major proportion of anal canal malignancies in China [4]. However, no standard therapeutic modality has been established to date. Being a rare disease in Western countries, oncologists preferred to manage it as SCC. Belkacem et al. [21] observed a survival benefit with CRT from a retrospective study of 86 adenocarcinoma cases; however, a patient distribution bias existed between different treatment groups. Subsequently, a high rate of local failure and distant metastasis was observed. Accumulated evidence supported APR might be necessary.

In a retrospective analysis of 165 anal canal adenocarcinoma patients by Kounalakis et al. [22], the APR group had significant improvement in OS compared with the radiation-alone group with a 5-year OS of 58%. Meanwhile, a relatively high rate of local recurrence was related to the necessity of radiation for adenocarcinoma [3]. Papagikos et al. [23] suggested preoperative CRT followed by APR and adjuvant chemotherapy. Currently, an APR-based multidisciplinary modality is the main treatment choice. Concurrent preoperative CRT followed by APR is widely performed in clinical practice. In our study, the major proportion of adenocarcinoma patients (N= 95, 73.6%) received APR-based therapy, whereas concurrent CRT was rarely performed (N=3, 2.3%). The 5-year OS rate was 40.6% for adenocarcinoma patients, a result that was clearly inferior compared to previously published Western reports with a median 5-year OS rate of 60% (range 58–63%) [1,3,21,22]. This survival inferiority might be due to a few reasons: on the one hand, 3 of our 4 centers were not cancer-specific hospitals and lacked radiation equipment for a long period of time, leading to insufficient use of radiation that was important for local tumor control; on the other hand, necessary imaging examinations for staging, including ultrasound colonoscope (5.7%), CT (18.4%) and MRI (16.7%), were rarely performed in the past, leading to insufficient information being provided to doctors for treatment planning. Future prospective studies are warranted to establish the most appropriate therapeutic options for the rare disease of anal canal malignancy.

Conclusions

Our results showed that adenocarcinoma was the major histological subtype in Chinese patients with anal canal malignancies. APR-based combined modality treatment was the first-choice treatment used in the past two decades, whereas multidisciplinary treatment was not performed adequately. The management of SCC must be standardized in China. In the future, randomized clinical trials are warranted to establish the optimal treatment options for anal canal adenocarcinoma patients.

Authors' contributions

PS, YHL and LYW: made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. PS and YHL: drafted the article and revised it critically for important intellectual content. PS, YHL, WW, CQC and LYW: responsible for final approval of the manuscript. All authors read and approved the final manuscript.

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