Anal canal malignancies: a review in an Asian population

Wong M T C, Lim J F, Eu K W

ABSTRACT

Introduction: Anal canal malignancies are rare tumours of the gastrointestinal tract that represent less than five percent of anorectal malignancies.

Methods: We retrospectively reviewed patients with anal canal malignancies who were treated from April 1989 to December 2008. Patients were identified from a prospective database and records were analysed for age, gender, presenting symptoms, duration of symptoms, mode of diagnosis, histological subtypes, stage of disease, treatment received, duration of follow-up, recurrence rates and survival.

Results: A total of 61 patients were treated for anal canal malignancies, comprising 2.1 percent of all anorectal malignancies treated during the same period. There were 31 male and 30 female patients, with a median age at diagnosis of 61 (range 38–83) years. The commonest presenting symptoms were per rectal bleeding (69.4 percent) and pain (33.9 percent). The commonest histology was adenocarcinoma (50.8 percent) and squamous cell carcinoma (SCC) (40.3 percent). Patients underwent either surgery, radiotherapy, chemoradiation or a combination of modalities. The median duration of follow-up was 28 (range 1–120) months. Five patients developed recurrences after a median of 23 (range 2–36) months. The five-year overall survival and disease-free survival was 65.5 percent and 63.7 percent, respectively, with SCC showing a trend toward a better prognosis.

Conclusion: Anal canal tumours are a rare clinical entity. They are usually present in the elderly with per rectal bleeding. They are usually treated using a multimodality approach, after the accurate establishment of histological diagnosis, which can yield reasonable survival rates.

Keywords: adenocarcinoma, anus, Asian, carcinoma, recurrence, squamous cell, survival

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INTRODUCTION

Anal canal malignancies are rare tumours that represent less than 5% of anorectal malignancies. They are 20–30 times less common than colon carcinoma.[1] The age range reported is highly variable, with the peak incidence during the seventh decade of life. Most case series report a predominance of female patients, with a ratio of five to one.[2-4]

The variation in anatomical definitions of anal canal malignancies in the literature has hindered valid comparison across studies, and has often led to confusion regarding optimal diagnosis and treatment. The natural history and treatment of anal canal malignancies, however, does differ from that arising from the anal margin, and the two should thus be considered as separate clinical entities. In this review, we discussed anal canal malignancies as they are more common, making up more than three-quarters of all anal tumours.[1]

Despite the much lower incidence of anal canal malignancies compared with their colorectal counterparts, they are still often associated with significant morbidity from both the disease itself as well as the treatment. Traditionally, anal canal malignancies were treated with sphincter-sacrificing surgery. In the 1970s, Nigro et al revolutionised the management of such tumours by demonstrating that combined-modality chemoradiation therapy (for squamous cell carcinoma, in particular) achieved survival and recurrence rates equivalent to those achieved with surgery, with the added advantage of preserving sphincter function.[5,6]

The current study reviewed a consecutive series of patients with malignancies of the anal canal, who were treated in our department over a 20-year period. Our aim was to review our department's experience in the management of anal canal malignancies, identify the spectrum of pathology, and analyse the treatment modalities and outcomes of these patients.

METHODS

We retrospectively reviewed patients with anal canal malignancies who were treated in the Department of

Table I. Patient and tumour characteristics.

	No.(%)
Patient characteristics	
Total no.	61 (100)
Male:female	31:30
Median; range (yrs)	61; 38–83
Median follow-up; range (mths)	28; 1–120
Tumour characteristics	
Histology	
Adenocarcinoma	31 (50.8)
Squamous cell carcinoma	25 (41.0)
Others	5 (8.2)
TNM Stage	
1	9 (14.8)
2	20 (32.8)
3	27 (44.3)
4	5 (8.20)

TNM: Tumour, Node, Metastases

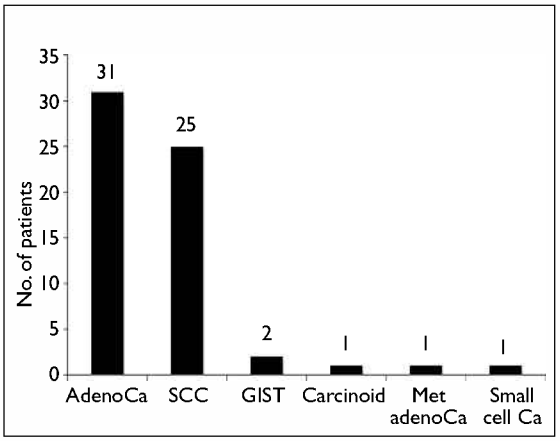

Fig. 1 Bar chart shows the distribution of histology.

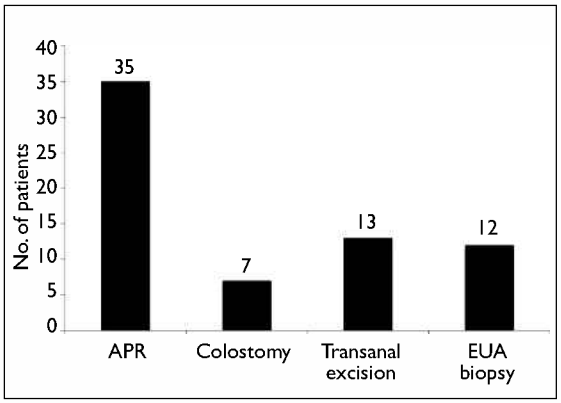

Fig. 2 Bar chart shows the types of surgical procedures.

Colorectal Surgery at the Singapore General Hospital from April 1989 to Dec 2008. Patients were identified from a prospective database and records were then retrieved from the medical records office. In this review, anal canal malignancies were defined as extending from below the anorectal junction down to the anal verge, as recommended by both the Union Internacional Contra la Cancrum and World Health Organization.[7,8] Low rectal tumours extending distally into the anal canal were excluded from the study. All histological subtypes were included for analysis except for melanomas, as the latter subgroup of patients had previously been reported in a paper published by our department.[9]

Patient data was analysed for the following variables: age, gender, presenting symptoms, duration of symptoms, mode of diagnosis, histological subtypes, stage of disease (according to Tumour, Nodes, Metastases [TNM] classification from the American Joint Committee on Cancer Manual for Staging of Cancer),[10] treatment received, duration of follow-up, recurrence rates and survival. The Kaplan-Meier method was used to calculate the five-year survival rates, and log-rank analysis was used for comparison between groups, with $p < 0.05$ being statistically significant.

RESULTS

In the 20 years spanning April 1989 to Dec 2008, we treated a total of 61 patients for anal canal malignancies (excluding anal melanomas). This represented 2.1% of all patients with anorectal malignancies seen during the same period (61 of 2,904 patients). Table I shows a summary of the patient and tumour characteristics.

Among the 61 patients, there was a slight male predominance (31 male vs. 30 female). The median age at the time of diagnosis was 61 (range 38–83) years. The commonest presenting symptoms were per rectal bleeding (69.4%), pain (33.9%) and an anal lump (32.3%). Less common symptoms included a change in bowel habits (e.g. constipation and tenesmus [19.4%]) as well as chronic perianal fistulation and sepsis (8.1%). Up to two-thirds (66.1%) of patients had a combination of symptoms, most commonly per rectal bleeding and pain. The median duration of symptoms was three (range 1–120) months. The malignancies were confirmed by biopsies, either during examination under anaesthesia (64.5%) or during endoscopy (colonoscopy or sigmoidoscopy). The commonest histology was adenocarcinoma in 31 (50.8%) patients and squamous cell carcinoma (SCC) in 25 (41.0%) patients. There were also two cases of gastrointestinal stromal tumours (GIST), one case of carcinoid tumour, one case of metastatic adenocarcinoma from a primary breast carcinoma and one case of undifferentiated (small cell) carcinoma (Fig. 1).

At the time of diagnosis, the majority of patients were in the advanced stages of the disease, i.e. TNM Stage 3 or 4 (52.5%). The type of treatment received varied, depending on the underlying histology, stage of

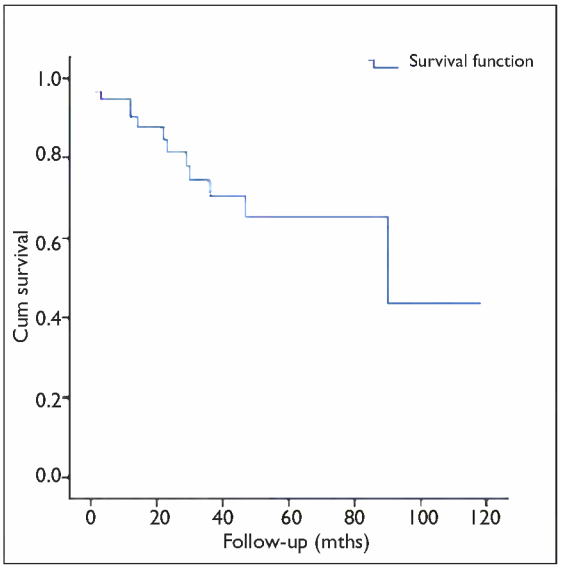

Fig. 3 Kaplan-Meier survival curve shows the overall survival.

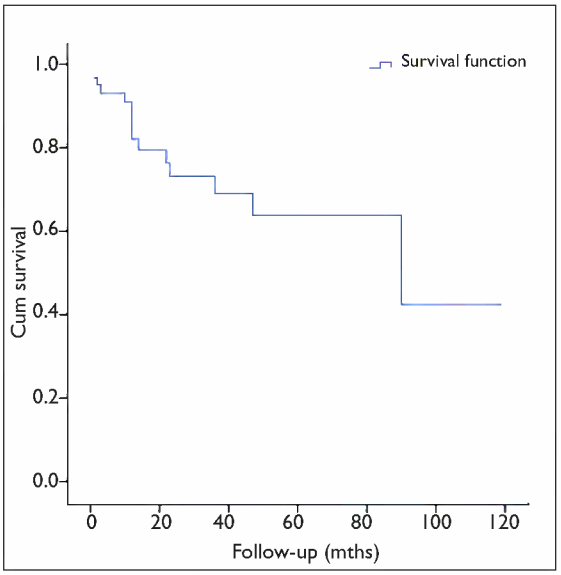

Fig. 4 Kaplan-Meier survival curve shows disease-free survival.

disease and the overall health of the patient. The patients either underwent surgical procedures, radiotherapy, chemoradiation therapy or a combination of treatment modalities. The types of surgical procedures performed are shown in Fig. 2. Among the 31 patients with adenocarcinomas, 15 underwent abdominoperineal resection (APR), 15 underwent surgery (nine APR and six transanal excision) followed by chemoradiation, and the remaining patient was too ill for any procedure. Among the 25 patients with SCC, 13 underwent definitive chemoradiation, 12 underwent surgery (seven transanal excision and five APR) and four underwent salvage APR after chemoradiation either for residual disease or for recurrence.

Both patients with GIST underwent APR and were doing well on follow-up. The patient with carcinoid tumour defaulted follow-up following diagnosis, while the patient with small cell carcinoma had disseminated disease at presentation and underwent palliative chemotherapy, but succumbed within four months of diagnosis. The patient with metastatic breast carcinoma underwent palliative chemoradiation and survived a further 36 months before succumbing to disseminated breast carcinoma. The median duration of follow-up was 28 (range 1–120) months. Of the 61 patients, 33 (54.1%) were still on follow-up when this study was being written, with 12 patients having defaulted and 16 having succumbed to the disease. In total, five patients developed recurrences after a median of 23 (range 2–36) months. The five-year overall survival (OS) was 65.5% (Fig. 3) and the five-year disease-free survival (DFS) was 63.7% (Fig. 4). Subgroup analysis revealed that compared to patients with adenocarcinoma, those with SCC had a more favourable five-year OS (73.6% vs. 62.1%, p = 0.81) (Fig. 5) and five-year DFS (70% vs. 51.7%, p = 0.67) (Fig. 6), but this was not statistically significant.

DISCUSSION

The rarity of anal canal malignancies compared to their colorectal counterparts has resulted in a relative paucity of studies regarding this disease in the literature. In this series, the 61 patients who were identified represented 2.1% of all anorectal tumours treated during the period of review, a finding consistent with the current literature estimate of 1%–5%.[1] Anal canal tumours usually present in the seventh decade of life and have been shown to have a marked female predominance, with a female-male ratio of about five to one.[2,3] Similarly, our patients presented at a median age of 61 (range 38–83) years, but there was a fairly equal distribution between the genders (31 male and 30 female).

Of the many histological subtypes, up to 80% of anal canal tumours are SCC.[11] The variants include cloacogenic, basaloid and transitional tumours, as they all exhibit a similar natural history, response to treatment and prognosis.[12,13] Adenocarcinomas account for up to 15% of anal cancer tumours, while the remaining constitute rarer subtypes such as melanomas, leiomyosarcomas and carcinoid tumours.[12] The distribution of histological subtypes in this series was different from that reported in the literature, with adenocarcinomas accounting for approximately half (50.8%) of the cases and squamous cell carcinomas being the next most common (41%).

As in most cancers, the multifactorial aetiology of anal canal cancer suggests an interaction between genetic and environmental factors.[11] Several predisposing factors

have been identified, including recurrent deletions of chromosomes 11q and 3p, previous anorectal irradiation, chronic anal fistulae, immunosuppression (human immunodeficiency virus and transplant patients), anal intercourse and smoking. In particular, SCC of the anal region has been shown to be closely related to anal warts and cervical carcinoma. The common aetiological factor linking these diseases is infection with the human papillomavirus (HPV), with up to 70% HPV prevalence rates reported in patients with SCC.[14,15] In contrast, HPV is rare in adenocarcinoma of the anal canal. It is suggested that infection with HPV (especially serotypes 16 and 18) results in chromosomal mutations, leading to chromosomal instability and the conversion of premalignant growths into invasive ones.[16] In a recent meta-analysis, the crude prevalence of HPV in healthy women was reported to be higher in North America (13.8%) and Northern Europe (8%), compared to Southeast Asian countries (6.2%).[17] In this series of Asian patients, none had cervical carcinoma or anal warts, and neither did they have a history of immunosuppression or anorectal irradiation, all of which could have accounted for the smaller proportion of patients with SCC compared to other series that reported mainly on Caucasian populations. Our findings are similar to those found in a study done in Hong Kong, in which 38.9% of tumours were adenocarcinomas and 44.4% were SCC.[13] The authors also explained that this higher incidence of adenocarcinomas could be attributable to the lower local prevalence of HPV infection in Southeast Asia compared to the Western world and that the role of HPV oncogenesis in anal tumours in the Chinese population required further study.[13] With melanomas being excluded from analysis, the proportion of adenocarcinomas in the current series was also naturally higher.

The majority of patients (70%–80%) usually present with nonspecific symptoms.[12] The coexistence of benign conditions such as haemorrhoids, fissures, fistulae, leukoplakia and Paget's disease adds to the challenge of accurate diagnosis. Patients often present with a combination of symptoms, most commonly bright red per rectal bleeding, pain, anal discharge and pruritus. Rarer symptoms such as incontinence, fistulation and pelvic pain are often sinister signs of more advanced disease. Similarly, the commonest symptom in our series was per rectal bleeding (69.4%) and pain (33.9%), with more than half the patients (66.1%) presenting with a combination of these two symptoms.

Fortunately, the distal location of anal canal cancers affords easy clinical evaluation. Examination should thus include a digital rectal examination, anal proctoscopy and palpation of the inguinal lymph nodes. This initial assessment allows one to gauge the size and fixity of the tumour. A transanal biopsy can be performed for histological confirmation. Endoanal ultrasonography provides further information about the depth of the lesion, involvement of the sphincter complex and perirectal lymphadenopathy, although it is highly operator dependent. Computed tomography and magnetic resonance imaging are useful for completing the staging process, or in situations where a stenotic or bulky lesion renders ultrasonography too uncomfortable. Anal canal cancer is primarily a locoregional disease, which rarely (10% of cases) metastasises to distant sites. Anal canal malignancies may spread to either the inguinal or the pelvic lymph nodes, with an overall incidence of clinically positive inguinal lymph nodes being 10%–20%.[12] In this series, clinically positive inguinal lymph nodes were detected in 19% of our patients and only 8.2% had distant metastases (TNM Stage 4).

SCC represents the majority of anal canal tumours. Prior to the revolutionary work by Nigro et al in the 1970s,[5] APR and permanent colostomy were the mainstay of treatment, with five-year survival rates of 38%–71% and recurrence rates of 27%–43%.[1-3] The subsequent introduction of definitive chemoradiation as the primary treatment resulted in survival and recurrence rates similar to those for surgery but with the added advantage of sphincter preservation in up to 80% of patients.[18] Based on the results of three large randomised controlled trials,[19-21] the recommended first-line treatment of anal canal cancer is radiation with 5-fluorouracil (with at least 45-Gy) and mitomycin, with the inguinal lymph node basin typically included within the radiation field; this has yielded five-year survival and recurrence rates of between 58%–90% and 7%–19%, respectively.[22-24] Surgery is now usually reserved for patients with incomplete response to chemoradiation therapy or those requiring salvage surgery for recurrent disease. In our series, survival outcomes compared favourably with those in other published series, with five-year OS for SCC at 73.6% and five-year DFS at 70%.

Adenocarcinoma of the anus is rare, representing only 3%–9% of anal carcinomas.[25] These cancers more commonly result from downward spread of a low rectal cancer; however, the latter group was excluded from this study. Adenocarcinoma may occasionally arise from the anal glands or develop in a chronic fistula. Radical resection with or without neoadjuvant or adjuvant chemoradiation is usually required. Adenocarcinoma of the anal canal was the predominant histological

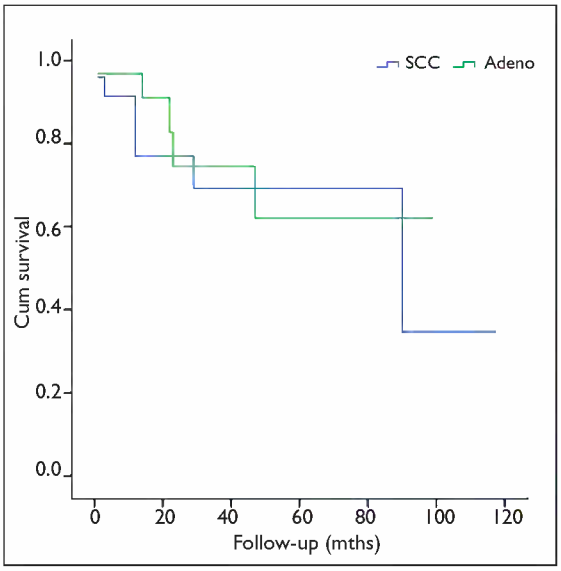

Fig. 5 Kaplan-Meier survival curve shows the overall survival by histology.

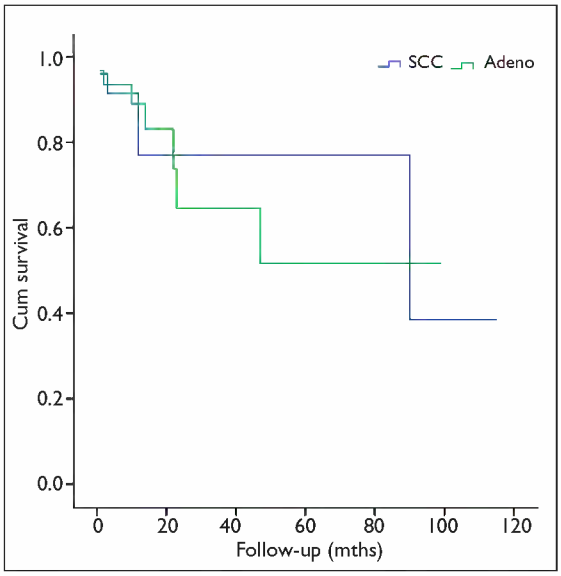

Fig. 6 Kaplan-Meier survival curve shows disease-free survival by histology.

type in our series (50.8%). Of these 31 patients, 25 underwent APR with or without chemoradiation postoperatively, and the remaining six underwent local excision and adjuvant chemoradiation. Compared to our patients with SCC, 14 (56%) underwent definitive chemoradiation, 12 underwent surgery (seven transanal local excision and five APR) and four underwent salvage APR after chemoradiation either for residual disease or for recurrence. In the latter group of patients, three of the four patients were alive and doing well on follow-up at the time of writing this study. We acknowledge that the salvage rate is high, possibly explained by the heterogeneity of chemoradiation protocols stretched over the 20-year study period. In addition, a recent review of the literature showed that up to 33% of patients would have treatment failure after initial chemoradiation, either in terms of residual disease or recurrence, with salvage APR being the treatment of choice when there is no disseminated disease elsewhere.[26]

The reported prognosis in patients with anal canal adenocarcinomas has been uniformly poor and the trend was similar in our series,[25,27] with five-year OS at 62.1% and five-year DFS at 51.7%, both of which were consistently poorer than those for patients with SCC. The two patients with GIST underwent APR and were disease-free on follow-up, suggesting that this subgroup of patients often do well with surgery and close follow-up. As expected, patients with metastatic breast adenocarcinoma and undifferentiated small cell adenocarcinoma fared poorly due to disseminated disease at the time of presentation. Unfortunately, the small number of patients did not permit feasible statistical comparison to be made based on treatment methods and T-stage. Transanal local excision in carefully selected cases can provide excellent survival and local control for patients with tumours that are small (up to 1 cm), in the distal anal canal and do not infiltrate the sphincter.[12] Many series in the literature, including our own, have employed varied doses of radiation and chemotherapeutic agents, which has made comparisons difficult.

In conclusion, this report represents the most comprehensive review of the management of anal canal tumours locally. The results of our review support the use of chemoradiotherapy as primary therapy for patients with SCC of the anal canal, as more than half of the patients underwent this modality of treatment, and together with those undergoing initial APR, achieved a favourable five-year OS of more than 70%. Carefully selected small tumours can be managed with local excision when the patient is closely followed up. Salvage APR for persistent or recurrent disease results in encouraging survival rates for selected patients. Adenocarcinoma of the anal canal can be managed with surgery alone and with the use of postoperative chemoradiotherapy for selected patients, yielding good results, albeit somewhat poorer than those with SCC. GIST can also be effectively managed with surgical resection and close follow-up, while undifferentiated small cell variants tend to do poorly.

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