Anorectal melanoma: not a haemorrhoid

Greg Turner, Sarah Abbott, Tim Eglinton, Chris Wakeman, Frank Frizelle

Abstract

Aim Melanoma of the anorectum is a rare malignancy which is particularly aggressive compared to cutaneous melanoma. Due to its presenting symptoms, location and rarity there is often a delay in diagnosis. The purpose of this paper is to raise awareness of anorectal melanoma in New Zealand by presenting our institution’s experience of four cases.

Methods The presentation, management and outcomes of four cases are described. A review of the literature surrounding anorectal melanoma was also carried out.

Results The four cases (3 male, 1 female, aged 30–87 years) all presented with haemorrhoidal symptoms of anal discomfort and/or outlet rectal bleeding. Three patients had metastatic disease at presentation, and the remaining patient was found to have a concurrent lymphoma which was treated with chemotherapy before he underwent excision of the melanoma. Surgical excision is the mainstay of treatment and recent literature suggests transanal excision of the primary tumour to have equivalent overall survival to abdominoperineal resection.

Conclusion Anorectal melanoma is rare tumour with a poor prognosis. Patients are commonly misdiagnosed as having haemorrhoids; therefore a high index of suspicion is needed to enable early diagnosis. Metastatic disease is common at presentation, and the key prognostic indicator. Local control can be obtained with transanal excision, avoiding the morbidity of abdominoperineal resection. Adjuvant therapies available at present provide little survival advantage.

Melanoma is commonly thought of as a skin cancer however it may also affect the mucosal surface. Anorectal melanoma is a rare mucosal malignancy which displays particularly aggressive tumour biology compared to cutaneous melanoma.

Due to the location, rarity and variable appearance there is often a delay before the diagnosis is made. Many patients present with rectal bleeding and/or anorectal discomfort, and are often misdiagnosed with haemorrhoidal disease. Thirty percent of anorectal melanomas are unpigmented, contributing to misdiagnosis. Patients may also present with palpable inguinal lymphadenopathy.

The mainstay of treatment is surgery, with abdominoperineal resection historically being the procedure of choice. More recently, with the acknowledgment of the very poor prognosis, trans-anal excision (with or without local radiotherapy) has been shown to provide equivalent oncological outcomes with less morbidity and better quality of life. Survival rates are directly related to stage of disease; and regardless of the extent of resection, the prognosis remains dismal.
We present four cases that have been treated at our institution over 12 years. The aim of this paper is to raise awareness of this rare condition and describe new directions in therapy.

Case reports

The four cases to be described are summarised in Table 1 below.

**Table 1. Patient demographics and outcomes**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis</th>
<th>Gender</th>
<th>Stage at diagnosis†</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>A</td>
<td>87</td>
<td>Male</td>
<td>II</td>
<td>Died of disease 13 months after diagnosis</td>
</tr>
<tr>
<td>B</td>
<td>65</td>
<td>Female</td>
<td>III</td>
<td>Alive with metastatic disease 7 months after diagnosis</td>
</tr>
<tr>
<td>C</td>
<td>81</td>
<td>Male</td>
<td>I</td>
<td>Died disease-free 5 years after diagnosis</td>
</tr>
<tr>
<td>D</td>
<td>30</td>
<td>Male</td>
<td>III</td>
<td>Alive with metastatic disease 1 month after diagnosis</td>
</tr>
</tbody>
</table>

† Staging as described by Iddings et al6:
I: Localised disease
II: Regional lymph node involvement
III: Distant metastases

**Patient A** is an 87-year-old male who presented with several months of anal discomfort with associated bleeding per rectum. On examination there was a small mass arising from the anal canal. He underwent examination under anaesthesia and excision biopsy of a presumed anal cancer. Histology confirmed malignant melanoma.

Staging computed tomography (CT) of the abdomen and pelvis and magnetic resonance imaging (MRI) of the pelvis identified left inguinal lymphadenopathy, but no lymphadenopathy in the mesorectal or pelvic nodes. Subsequent fine needle aspiration (FNA) confirmed metastatic melanoma to the left inguinal region. After discussion at the Colorectal Oncology Multidisciplinary Meeting (CMDM) he received radiotherapy to the anus and underwent left inguinal lymph node dissection.

Restaging PET-CT performed 4 months after diagnosis revealed two new large metastatic left external iliac nodal masses. He received radiotherapy to this area.

Eleven months following diagnosis he developed visible melanoma deposits in the right buttock and perineum, as well as a lesion in the T7 vertebra causing spinal cord compression. He received further palliative radiotherapy to these regions.

Unfortunately his disease continued to progress and he died 13 months after diagnosis.

**Patient B** is a 65-year-old female who presented with rectal bleeding and a sensation of prolapse over approximately twelve months. She was initially diagnosed with haemorrhoids and colonoscopy revealed a 2 cm polyp 1–2 cm from the anal verge.

She underwent transanal excision. Histological examination revealed malignant melanoma. Staging CT revealed an enlarged right inguinal node and a mesorectal
node, as well as multiple pulmonary and hepatic metastases. After discussion at the CMDM she was referred to Medical Oncology where she was considered for a clinical trial of ipilimumab. Unfortunately her disease progressed rapidly prior to commencing the trial and at 7 months after diagnosis is not undergoing any further treatment.

**Patient C** is an 81-year-old man who presented with anal discomfort and itch to his GP, who was concerned and referred the patient to a plastic surgeon, who subsequently referred the patient on to a colorectal surgeon.

Colonoscopy revealed a pigmented butterfly-shaped lesion in the anal verge expanding into the anal canal (Figure 1). Biopsy confirmed invasive melanoma. Staging CT showed a large subcarinal mass and further lesions within the spleen and left kidney. FNA of the chest lesion revealed non-Hodgkin lymphoma.

After discussion at the CMDM he underwent R-CHOP\(^3\) chemotherapy to treat the lymphoma with a view to delayed surgical resection of the melanoma. He responded well to chemotherapy and underwent trans-anal excision 10 months after diagnosis. Histology showed melanoma *in situ* but no residual invasive melanoma, consistent with regressed malignant melanoma.

He remained under close clinical follow-up and restaging investigations at 1 year showed remission of the lymphoma and no evidence of metastatic melanoma. He died of other causes 5 years after diagnosis.

**Figure 1. Photograph of Patient C demonstrating a pigmented lesion arising from the anal verge extending into the anal canal (biopsy confirmed invasive melanoma)**
Patient D is a 30-year-old male who presented with a 9-month history of fresh per rectal (PR) bleeding and rectal pain. He was diagnosed with haemorrhoids and referred for a surgical opinion at which point it was noted he had a pedunculated rectal polyp. He underwent colonoscopy which showed no further bowel pathology. Biopsy of the polyp revealed malignant melanoma. He underwent transanal excision for diagnostic and therapeutic purposes. At surgery it was noted to be approximately 3 cm in size, pedunculated and arising from the anorectal junction. The histology is demonstrated in Figure 2.

Figure 2. Low magnification micrograph of polyp demonstrating extensive infiltration of anorectal mucosa and the submucosal stalk (the malignant cells are positive for Melan-A and SOX-10 immunohistochemical stains in keeping with malignant melanoma)

Postoperatively he underwent a staging CT which showed extension of the primary tumour into the right mesorectal fat with surrounding local lymph nodes, extensive hepatic metastatic disease (Figure 3) as well as possible small bowel and pulmonary metastases. The patient was referred to Medical Oncology and intends to participate in a clinical trial of ipilimumab.
Discussion

Anorectal melanoma is a rare tumour, accounting for less than 1% of all colorectal malignancies\(^4\). It was first described in 1857 by Moore\(^5\) and accounts for only 2% of all melanomas, yet is the third most common primary location for such tumours, surpassed only by skin and eyes.\(^4\) Between 22–30% of anorectal melanomas are amelanotic and this is associated with a worse prognosis.\(^1,2\)

The overall prognosis for anorectal melanoma is poor. Cagir et al\(^4\) reported 177 cases of anorectal melanoma from the SEER database diagnosed between 1973–1992. They found anorectal melanoma accounted for 0.05% of all colorectal tumours diagnosed in that period, and demonstrated overall survival rates of 56% and 15% at one and five years respectively, with a mean overall survival of 15 months.

This condition occurs most often in the 6\(^{th}\) and 7\(^{th}\) decades of life, and despite our patient series, there is a reported higher rate in females (2.2:1).\(^6\)

Patients most commonly present with rectal bleeding and/or anal discomfort, and are commonly misdiagnosed as having haemorrhoids.\(^2,7\)

**Staging**—Melanoma is excluded from the AJCC staging system for anal cancers.\(^8\) Some series\(^6\) stage disease as localised (stage I), regional lymph node involvement (stage II) or distant metastatic disease (stage III).

Between 15 and 24% of patients have distant metastases at the time of diagnosis,\(^4,9\) similarly there is an even higher rate of regional lymph node involvement.\(^4\)

Iddings et al\(^6\) described the prognostic significance of lymphatic metastases. They reported 142 cases of anorectal melanoma, of which 60% had localized disease at
presentation, 19% with regional lymph node involvement, and a further 21% with distant metastases.

Outcome was directly related to disease stage, with median survival of 24 months, 17 months and 8 months respectively (Table 2). Furthermore they reported mesorectal lymph node involvement to be uncommon, with most lymphatic disease found in the inguinal regions.

**Table 2. Survival outcomes of anorectal melanoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median survival (months)</th>
<th>5-year survival</th>
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<tbody>
<tr>
<td>I</td>
<td>Localised disease</td>
<td>24</td>
</tr>
<tr>
<td>II</td>
<td>Regional lymph node involvement</td>
<td>17</td>
</tr>
<tr>
<td>III</td>
<td>Distant metastatic involvement</td>
<td>8</td>
</tr>
</tbody>
</table>

Survival outcomes for Anorectal Melanoma by stage for 143 patients, Iddings et al.

**Anatomic considerations**—Bello et al.\(^9\) report little effect on prognosis whether the melanoma arises from the rectum, anorectal transitional zone or the anus. Tumours arising from the rectum and anorectum had a median Breslow thickness of 12mm and 8mm respectively, compared to a median Breslow thickness of 6.5mm in those arising from the anus.

Nearly two-thirds of tumours in the rectum or anorectum recurred systemically, whereas anal melanomas more often recurred in the regional lymph nodes. Overall median survival was 27 months for rectal tumours, 28 months for anorectal tumours, and 22 months for those arising from the anus. There was no statistically significant difference between survival or recurrence with anatomic location.

**Surgical treatment**—The primary treatment modality for anorectal melanoma is surgery. There has been some debate in the literature regarding the procedure of choice. Abdominoperineal resection (APR) is commonly performed, but more recent evidence has shown trans-anal excision (TAE) to offer equivalent survival with significantly less morbidity.\(^2,6,9,11\)

In view of the higher prevalence of inguinal rather than mesorectal lymph node metastases, some advocate sentinel lymph node biopsy alongside TAE.\(^12\) This approach is well established in the management of cutaneous melanoma but it’s role in anorectal melanoma is less clear,\(^13–15\) however PET-CT may be more helpful and less invasive.

Series reporting TAE have not observed high rates of isolated local recurrence.\(^16–18\) Yeh et al.\(^19\) report the rate of isolated local recurrence is comparable regardless of whether undergoing TAE or APR. They hypothesise systemic dissemination is an early event in tumorigenesis so by the time the primary lesion is clinically apparent, micrometastases are well established. Pessaux et al.\(^2\) advocate APR for salvage surgery in the rare instance of isolated local recurrence.

**Adjuvant therapy**—Radiotherapy and chemotherapy are generally reported to be of limited value in anorectal melanoma.\(^2,9\) Radiotherapy may have a role in local control as shown in patient A.
Kelly et al\textsuperscript{20} report radiotherapy having a role in maintaining local control following sphincter preserving surgery, however found little benefit for overall survival. Hay et al\textsuperscript{21} describe one case of an elderly patient deemed unfit for surgery who underwent external beam radiotherapy with an excellent response, with no signs of recurrence or distant spread at 12-month follow-up.

**Targeted therapies**—A better understanding of the molecular pathogenesis of mucosal melanoma (including anorectal melanoma) is leading to development of potential targeted therapies, particularly to slow progression of advanced disease. A proportion of mucosal melanomas will have an identifiable mutation in BRAF or KIT genes (both recognised proto-oncogenes), however the rate is significantly lower than cutaneous melanoma.\textsuperscript{22}

Small trials have shown a potential role for imatinib (a tyrosine kinase inhibitor) in those with an identified KIT gene mutation, with 23–54\% of patients with metastatic melanoma showing partial response.\textsuperscript{23,24}

Vemurafenib (a BRAF inhibitor) has shown improved survival in metastatic cutaneous melanoma, however there is no evidence for its use in mucosal melanoma at present.\textsuperscript{25}

Ipilimumab (a monoclonal antibody directed at CTLA-4—thought to be a tumour-associated antigen) has been investigated for treatment of metastatic mucosal melanoma,\textsuperscript{26} however the response to treatment has not been dramatic in studies conducted to date.

**Conclusion:**

Anorectal melanoma is a rare tumour with a poor prognosis. Patients are commonly misdiagnosed as having haemorrhoidal disease and a significant number of lesions are amelanotic, therefore a high index of suspicion is needed to enable early diagnosis and treatment while the lesion is still potentially curable.

Metastatic disease is common and is the key determinant of overall survival. Local control can be effectively achieved with transanal excision, sparing patients the morbidity of abdominoperineal resection. Adjuvant systemic therapy options available at present provide little survival advantage.

**Competing interests:** Nil.

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