

# 22 Mucosal melanoma

Melanomas arising from mucosal surfaces are very rare tumours and can present formidable challenges for management of tumours which on the whole have a very poor prognosis. The recent finding that at least one third of mucosal melanomas over express the receptor kinase c-kit (compared to less than 5% of cutaneous melanomas) may have implications for treatment with imatinib.<sup>1</sup> Patients with mucosal melanoma should be strongly considered for referral to a major centre with experience in the management of these tumours.

## 22.1 Melanoma of the anorectal region

### 22.1.1 Background

Anorectal melanoma (ARM) is a rare condition comprising less than 1% of anorectal tumours. The rate appears to be similar between patients of different racial and ethnic backgrounds. Median age of onset is approximately 60, with a slight female preponderance. The common presenting symptoms are haemorrhoidal-type bleeding, mass or discomfort. Most series report that at least a third of anorectal melanomas are excised with a preoperative diagnosis of haemorrhoids. The characteristic appearance is of a polypoid lesion, frequently ulcerated, although sessile and flat lesions are also encountered. The majority of lesions appear to arise around the dentate line or below from the anal canal. A small proportion of lesions appear to arise from the rectal mucosa just above the dentate line. Melanomas occurring in normal skin outside the anal canal should be considered as cutaneous melanoma and treated appropriately. Although microscopically it appears that the majority of anorectal melanomas contain melanin, at least a quarter and possibly a greater percentage do not contain obvious melanin macroscopically. Many anorectal melanomas do not have the typical dark appearance of cutaneous melanoma.

At least 20% of patients will present with regional lymph node metastases. Another 20–40% will present with distant metastatic disease. The average tumour size is in the order of 3–4cm and there is often associated *in situ* change. The standard AJCC/UICC staging for cutaneous melanoma is not appropriate for anorectal melanoma as most tumours are greater than 4mm in thickness. Tumour thickness has not been shown to be a reliable predictor of outcome. Neither has the presence of nodal metastases, histological subtype or gender.

Preoperative evaluation should include staging with a CT chest, abdomen and pelvis. A case can be made for PET scanning if available. Endoscopic ultrasound to assess the depth of penetration of the tumour to identify patients who may be suitable for a limited procedure has been evaluated in a small number of cases.

### 22.1.2 Management

Traditionally, abdomino-perineal resection (APR) has been recommended for the management of ARM. More recent studies have indicated that the much lesser procedure of complete wide local excision of the primary melanoma with sphincter preservation is an option for many patients. The results for all series published after 1990 that compare patients undergoing surgical management and report more than ten patients are shown in Table 6.<sup>2-14</sup> Most but not all studies show a higher rate of local control for patients undergoing APR, but in all but one study no advantage in survival was shown for either APR or local excision. This is an old study from Memorial Sloan Kettering Cancer Center, however a more recent study from the same institution reported very similar rates of local control and overall survival for the two procedures from 1984–2003, when the standard of care switched from APR to WLE (see Table 6). Approximately one third of patients with operable (non-metastatic) anorectal melanoma will require an abdominoperineal excision for complete resection of the melanoma to be accomplished. The extent of margins for either APR or WLE has not been evaluated, although Ward et al aim to achieve a 2cm margin.<sup>15</sup> Remarkably, the width of excision is uncommonly reported in the literature.

Patients with established nodal metastases at presentation should undergo lymphadenectomy at the time of the definite surgical procedure for local control. The commonest site of regional node failure is the inguinal region. High rates of pelvic lymph node involvement have been reported at the time of APR in one series, but are uncommon in other series when reported.

Overall survival is not strongly associated with the presence of regional node metastases, most likely reflecting the very high risk of distant metastasis. For this reason elective inguinal lymphadenectomy is of no value and is not indicated. Sentinel node biopsy has been successfully performed in a small number of cases with limited follow-up. In view of the lack of a relationship between outcome and lymph node status and lack of evidence supporting its role, SNB cannot be recommended. It is unlikely that there will ever be sufficient numbers for a comprehensive evaluation of the procedure.

Lymphadenectomy is indicated at the time of the definitive procedure for primary ARM with proven regional lymph node involvement.

Older anecdotal reports of radiotherapy following limited excision reported contradictory results, however a recent series of 23 patients treated by wide excision and postoperative radiotherapy (30 Gy in five fractions over 2.5 weeks to the primary tumour and draining lymphatic sites) was achieved with minimal toxicity, a local control rate of 74%, and a five-year actuarial survival of 31% after a median follow-up of 37 months.<sup>16</sup> Local control in this report is similar to patients undergoing APR.

The experience of ARM is that the overwhelming majority of patients with anorectal melanoma will die of the disease, with most manifesting evidence of distant disease within two years of diagnosis. The commonest sites of metastases are lung (over 50%) followed by liver, brain and gastrointestinal tract. Distant metastatic disease is generally managed similarly to metastatic cutaneous melanoma. Radiotherapy may have a role for palliation of local, regional or distant recurrence.

The overall survival for ARM is poor. Patients with disease confined to the anal canal have a five-year survival of approximately 35% and a median survival of approximately 30 months. Patients with regional disease at presentation have a median survival of 20 months, and patients with metastatic disease at presentation rarely survive 12 months.

Evidence summary	Level	Reference
The only data to support recommendations for surgical therapy are small retrospective cohort studies with the potential for considerable bias. Nevertheless the results from these studies are consistent. In summary, wide local excision in many but not all series is associated with a higher rate of local recurrence than APR, but overall no advantage for survival with APR over wide local excision has been shown (see Table 6). The very high rate of distant failure and poor overall survival appears to be independent of local recurrence	IV	2–14

### Recommendations

	Grade
1. The primary lesion for melanoma of the anorectal region should be managed by sphincter preserving complete local excision in most cases. APR is indicated only for patients with loco-regional disease whose primary tumour cannot be resected by a limited procedure	<b>D</b>
2. Pelvic node failure as an isolated event is uncommon. Extended pelvic lymphadenectomy is not indicated	<b>D</b>
3. There is no evidence to support elective (as compared to therapeutic) inguinal lymphadenectomy	<b>D</b>
4. Sentinel node biopsy has been described in a small number of cases but there is no evidence to support its routine use at the present time	<b>D</b>
5. The role for radiotherapy (RT) in patients with close/involved margins after wide local excision or abdomino perineal resection is unknown but it may be considered	<b>D</b>
6. The care of patients with anorectal melanoma be undertaken by a multidisciplinary team experienced in the management of these patients	<b>D</b>

Table 6 summarises papers published since 1990 that have treated more than ten patients with locoregional disease only at presentation. Figures refer to patients from these papers treated by APR or WLE only. Survival figures in some instances have been obtained from Kaplan Meier plots in the papers. In many cases formal statistical comparison of APR and WLE survival curves were not performed, but if the authors concluded that there was no difference in survival the result has been summarised as a non-significant result (NS). In most papers the local recurrence rate was expressed as a simple fraction rather than a product limit estimate.

**Table 6**

**Studies comparing Abdomino-pelvic resection and sphincter preserving wide local excision for patients with localised anal melanoma (more than 30 patients and published since 1990)**

Author	Year	Time period	Number of patients APR, WLE	Survival % 5 yr, or median (months)	Local recurrence APR, WLE
Goldman <sup>2</sup>	1990	1970–1984	15,18	12m 13m NS	4/15 9/12
Slingluff <sup>3</sup>	1990	1974–1989	24,12	8% 7% NS	50% 100%
Ross <sup>4</sup>	1990		14,12	19% 20% NS	4/14 7/12
Antoniuk <sup>5</sup>	1993	1951–1991	4,8	29m 22m NS	2/4 5/8
Brady	1990	1929–1993	43,14	25% 8% P<0.05	not available
Konstadoulakis <sup>6</sup>	1995	1975–1991	8,5	0% 25% NS	50% 22%
Roumen <sup>7</sup>	1996	1960–1995	18,16	25% 58% NS	1/8 12/16
Thibbault <sup>8</sup>	1997	1939–1993	26,11	25% 39% NS	10% 28% NS
Moozar <sup>9</sup>	2003	1980–1999		7m 12m NS	not available
Bullard <sup>10</sup>	2003	1988–2002	4,11	25% 64% NS	50% 18% NS
Weyandt <sup>11</sup>	2003	1992–2002	5,11	NS no info	1/5 5/8
Malik <sup>12</sup>	2004	1983–2001	9,10	25m 20m NS	not available
Pessaux <sup>13</sup>	2004	1977–2002	9,21	33 16 NS	2/9 10/21
Yeh <sup>14</sup>	2006	1984–2003	19,10	34% 35% NS	21% v 26% NS

## 22.2 Mucosal melanoma of the head and neck

### 22.2.1 Background

Mucosal melanoma of the head and neck is a very rare tumour accounting for less than 1% of all head and neck melanomas. The median age of presentation is approximately 60 with a slight male predominance. Approximately 60% occur in the sino-nasal region, with two-thirds arising obviously from the nasal cavity. Virtually all the remainder occur in the oral cavity, particularly the upper jaw, apart from a very small percentage found in the larynx.

Nasal melanomas present with nasal obstruction or bloody discharge similar to sinus melanoma. Oral melanoma may present with a mass, an area of pigmentation, bleeding, or loosening of teeth. The standard AJCC staging system is not appropriate for mucosal melanoma. Lymph node involvement is unusual at the time of presentation and does not commonly occur among patients who develop local recurrence or distant disease.

### 22.2.2 Management

Because of the rarity of this tumour, treatment guidelines are not well established and consideration should be given to referral to a unit with expertise in managing head and neck melanoma. Recommendations for treatment are based on a limited number of small retrospective case series<sup>17–22</sup> with considerable potential for bias.

Overall survival remains poor with reported rates of survival varying from approximately 20% to less than 5% at ten years. A high rate of early haematogenous dissemination and late presentation compared to cutaneous melanoma may explain these poor results.

Evidence summary	Level	Reference
Complete surgical excision is the fundamental surgical aim but may be difficult to achieve without a destructive or disabling procedure. The addition of radiotherapy to surgery has not been shown to improve either local control or survival, apart from one small study which found a small improvement in local control	III-3	17-22
Primary radiotherapy alone has been advocated, but to date the series comparing it with surgery with or without radiotherapy show poorer local control and survival	IV	19

Recommendations	Grade
7. Patients with mucosal melanoma of the head and neck are best managed by complete surgical excision. Radiotherapy has not been shown to be of benefit to patients who have undergone a complete resection but may be of benefit in patients who have residual disease	<b>D</b>
8. Patients to be referred to a specialist unit with experience in head and neck melanoma	<b>D</b>

### 22.3 Melanoma of the oesophagus

A very small number of oesophageal melanomas have been reported in the literature, but as the gastro-intestinal tract is a potential site for metastasis from cutaneous melanoma, the true nature of many lesions is debated. Many patients present with disseminated disease. Tumours are often large at presentation and tend to be located in the distal third of the oesophagus. The majority of patients are dead within twelve months. Radical resection can be considered in patients with limited disease.

### 22.4 Melanoma of the male genito-urinary tract

Melanoma of the male external genitalia and lower urinary tract is a very rare tumour. Many patients have been aware of a pre-existing pigmented lesion. Melanomas of the glans penis arise in glabrous skin (no hair follicles or sweat glands) and behave similarly to vulval melanoma. Wide excision rather than penectomy (radical or partial) is appropriate if possible. Lymphadenectomy is indicated for involved inguinal lymph nodes. Sentinel node biopsy has been reported but there is not sufficient evidence to make any recommendation. Overall survival is poor, with most patients dying within three years.

In contrast, melanomas of the skin of the penis and scrotum behave similarly to cutaneous melanoma, but presentation is often delayed and results poorer than seen with cutaneous melanoma. Wide excision is indicated rather than penectomy. Again, a role for SNB has not been established.

## 22.5 Vulval melanoma

Vulval melanoma is a very rare condition accounting for less than 1% of all gynaecological malignancies. In contrast to cutaneous melanoma, the incidence of vulval melanoma appears to be stable or decreasing. It is typically a disease of elderly females (median age at presentation late sixties). Most patients report the presence of a mass and/or bleeding, while pruritus and pain are less common symptoms at presentation.

The commonest histological subtypes are mucosal lentiginous melanoma or nodular melanoma. Many lesions are ulcerated and typically 2–4mm in thickness. The regional lymph nodes are involved in up to one third of patients at presentation, and up to 25% of patients present with distant disease.

The skin of the perineum varies from hair-bearing skin over the labia majora to glabrous (non-hair-bearing skin) in the inner vulva to the mucosa of the vaginal introitus. Up to one third of vulval melanomas arise on the labia majora and are characteristically flat, pigmented lesions, while more centrally-based lesions, which frequently involve the labia minora and clitoris, are characteristically nodular, and up to one third may be amelanotic. Clark micro-staging is of no value for lesions arising in the mucosa or glabrous skin and Breslow thickness has been variably reported but is of significance. Several staging systems have been proposed, including a simple clinical staging system (stage I, local disease only; stage II, spread to regional lymph nodes; stage III, metastatic disease), although in one more recent study the AJCC staging system for cutaneous melanoma was the only factor predictive of recurrence-free survival in a multivariate analysis.<sup>23</sup>

Similar to cutaneous melanoma, prognostic factors associated with outcome include tumour thickness, ulceration and nodal status. In several reports amelanosis and age are also related to outcome. Overall the prognosis of vulval melanoma is poor, with 50% of patients surviving five years. Five-year survivals may be as high as 70% for patients with thin lesions (< 1mm) but less than 20% for patients presenting with regional lymph node involvement.<sup>24</sup>

### 22.5.1 Surgical management

Surgery remains the mainstay of treatment for vulval melanoma. There are little prospective data and no randomised studies to guide management due to the rarity of the disease. The surgical approach has evolved from aggressive surgery, for example bilateral vulvectomy with inguinal lymphadenectomy, to more limited procedures due to the recognition that extensive procedures, while providing a higher rate of local control, do not impact on overall survival but cause considerably more morbidity.<sup>23,25–30</sup>

Superficial lesions, particularly those in a favourable position, may be treated effectively by wide local excision. Unfortunately central lesions involving clitoris and urethra, which are often thicker, may require more aggressive procedures to obtain complete excision.

There is little evidence on which to make recommendations for the width of excision but in principle, for thinner lesions, limited excision margins are appropriate. A Swedish collaborative study reported a series of 281 patients with lesions < 2mm thick. The local recurrence rate was 1.8% and was not affected by margin sizes of 1–2cm versus 5cm.<sup>30</sup>

Elective lymph node dissection has not been shown to improve outcome but is associated with considerable morbidity. Sentinel node biopsy has been reported in vulval melanoma but its role is yet to be clarified.<sup>31</sup> The role of adjuvant radiotherapy is unknown but may be considered where resection margins are less than optimal. Radiotherapy may have a role for the patient who is unable or unwilling to undergo a surgical procedure.

Recurrent disease is best managed surgically, however most patients with recurrence also manifest evidence of distant disease. Management of distant disease, which has a similar pattern to cutaneous melanoma, should be similar to the management of disseminated cutaneous melanoma.

Evidence summary	Level	Reference
There are no randomised data and little prospectively collected data on which to base recommendations for treatment. Most series are small, collected over long time periods and retrospective. There appears to be no survival advantage to radical procedures over wide excision with modest margins of 1–2cm. There is no survival advantage for prophylactic lymphadenectomy and although sentinel node biopsy has been performed successfully for vulval melanoma, there are little data on its efficacy or safety at the present time	IV	23–30, 32

Recommendations	Grade
9. Histologically confirmed melanoma of the vulva be managed by wide excision with limited margins (1–2cm). Extensive lesions particularly those centrally located may require extensive/exenterative procedures. In the absence of proven regional lymph node spread lymphadenectomy is not indicated	<b>D</b>
10. Patients with vulval melanoma be referred to a specialist unit with expertise	<b>D</b>

## 22.6 Vaginal melanoma

Melanoma of the vagina and urethra is an extraordinarily rare condition. The lower third of the vagina is most commonly affected and patients invariably present with advanced disease. Complete surgical removal, if feasible, frequently requires a major exenterative procedure. The risk of local recurrence, regardless of the extent of surgery or treatment modality, for example RT, is very high and most patients succumb to a combination of locoregional and distant disease within a short time.

## 22.7 Good practice points

- Any suspicious lesions of the genital tract should be biopsied
- As there is a high incidence of systemic disease in these cases, a CT/PET scan is indicated prior to radical surgery

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