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Surgery and radiotherapy in the treatment of cutaneous melanoma

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Adequate surgical management of primary melanoma and regional lymph node metastasis, and rarely distant metastasis, is the only established curative treatment. Surgical management of primary melanomas consists of excisions with 1–2 cm margins and primary closure. The recommended method of biopsy is excisional biopsy with a 2 mm margin and a small amount of subcutaneous fat. In specific situations (very large lesions or certain anatomical areas), full-thickness incisional or punch biopsy may be acceptable. Sentinel lymph node biopsy provides accurate staging information for patients with clinically unaffected regional nodes and without distant metastases, although survival benefit has not been proved. In cases of positive sentinel node biopsy or clinically detected regional nodal metastases (palpable, positive cytology or histopathology), radical removal of lymph nodes of the involved basin is indicated. For resectable local/in-transit recurrences, excision with a clear margin is recommended. For numerous or unresectable in-transit metastases of the extremities, isolated limb perfusion or infusion with melphalan should be considered. Decisions about surgery of distant metastases should be based on individual circumstances. Radiotherapy is indicated as a treatment option in select patients with lentigo maligna melanoma and as an adjuvant in select patients with regional metastatic disease. Radiotherapy is also indicated for palliation, especially in bone and brain metastases.

Key words: cutaneous melanoma, electrochemotherapy, limb perfusion, melanoma radiotherapy, melanoma surgery, sentinel node

introduction

Surgery remains the mainstay of melanoma therapy at all sites. Early diagnosis combined with appropriate surgical therapy is currently the only curative treatment. Ideally, surgery should provide both local control of the disease and long-term survival without significant functional and/or aesthetic impairment. The aim of this article is to present updated recommendations on surgical management of melanoma.

surgery of primary tumour

biopsy

Skin lesions that might be melanoma should be referred using the ABCDE system (A, asymmetry; B, irregular borders; C, colour changes; D, diameter >5 mm; E, elevation) or the Glasgow system [1]. However, >50% of melanomas are *de novo* lesions that may not have any of the characteristics listed above. Clinical diagnosis can be improved by non-invasive epiluminescence microscopy (dermatoscopy) [2].

Excision biopsy is essential for accurate diagnosis and microstaging. This determines the choice of further therapy and provides important prognostic information. The pathology report should include the Breslow thickness (mm), presence of ulceration, mitotic index (0 or ≥1/mm^2), Clark level, lateral and deep margin size (mm) and the presence of local metastasis. Mitotic index is the third most important independent prognostic factor [3, 4], and will be introduced in the new AJCC staging system as a reporting standard. Regression, tumour-infiltrating lymphocytes, vertical growth phase, angiolymphatic invasion, neurotropism and histologic subtype may also be of value.

Excision biopsy is usually performed with a 2 mm lateral margin and a cuff of subdermal fat. Incisional or punch biopsy may be performed for lesions that are difficult to remove because of size or site. It is believed not to have detrimental effects if subsequent therapeutic surgery is performed within 4–6 weeks. Shave or curette-type biopsies should not be performed because they limit the amount and quality of specimen for pathological assessment. The initial biopsy scar should not compromise subsequent surgery; on the limb, it should be oriented along the long axis.

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radical surgery

Before the 1970s, margins of therapeutic excision ranged from 3 to >5 cm. However, since then, six randomised, prospective trials (Table 1) have evaluated the effect of width of excision margins on local recurrence rates and survival. Rates of local control have been similar in five of these studies, but one has shown a 25% increase in locoregional recurrence in patients with narrow margins. None have shown a survival disadvantage for narrower compared with wider radial excision margins in melanoma of any thickness, although most were not powered to detect this, and one has shown a trend toward reduced survival [5–7].

Three trials were conducted for melanomas thinner than 2 mm: the French Cooperative Group Trial [8] and the Scandinavian Melanoma Group Study [9] compared 2 cm with 5 cm margins, and the World Health Organization (WHO) Melanoma Program Trial 10 compared 1 cm and 3 cm margins [10]. None of these trials demonstrated a benefit for wider margins (Table 1).

For melanomas of intermediate thickness (1–4 mm), 486 patients in the Intergroup Trial [11, 12] were randomised to 2 cm or 4 cm margins. Local recurrence rates (2.1% compared with 2.6%, respectively) and overall survival (OS) rates were similar (79% compared with 81%, respectively). In the group of patients with 2 cm margins, skin grafts were necessary in only 11% of cases, as compared with 46% of cases in the group with 4 cm margins ($P < 0.001$). Two large trials were conducted in patients with melanomas thicker than 2 mm: the UK Melanoma Study Group (MSG) trial of 900 patients compared 1 cm and 3 cm margins and the Scandinavian trial of 936 patients compared 2 cm and 4 cm margins [13, 14].

In the UK MSG trial, OS was similar in both groups, although a 25% higher rate of locoregional recurrence was noted in the group with the narrow margin [hazard ratio (HR) 1.26, $P = 0.05$]. The Scandinavian trial, which randomised patients with melanomas >2.0 mm (pT3, pT4) between 2 cm and 4 cm margins, reported no differences in outcome for disease-free survival (DFS) or OS [5, 14].

There are fewer data for melanomas thicker than 4 mm, since disease in this thickness band is uncommon. A large, but non-randomised study [15] showed that excisions with margins wider than 2 cm do not have any impact on local recurrence rates, DFS and OS. The UK MSG and Scandinavian studies included patients with melanomas >4 mm [13, 14].

For melanoma not thicker than 1 mm, excisions with a 1 cm margin are sufficient. Recommendations about 1–2 mm thick invasive melanoma are less clear; however, many national guidelines indicate that a 1–2 cm margin is sufficient, especially in regions of anatomic constraint associated with anticipated functional or cosmetic deformities (e.g. face, distal part of limbs). For melanomas >2 mm, a 2 cm margin is appropriate. In all surgical trials of primary melanoma, depth of excision has always been to at least muscle fascia, and this is the recommended deep margin, since more superficial excision has not been shown to be equivalent. Deeper excision has not been shown to improve outcome [16, 17].

In summary, this means that in general, surgical management of primary melanoma consists of excision and primary closure.

special melanoma types

In certain subgroups of patients, recommendations on excision margins are based only on opinion.

For melanoma *in situ*, the recommended margin is 0.5 cm. Although thought to have no risk of metastasis, it can recur as *in situ* and then progress to invasive melanoma, and some data indicate that 1 cm margins may be required [18, 19].

Wider margins have been recommended for desmoplastic melanoma because of its increased tendency toward local recurrence. If this is due to contiguous subclinical spread, micrographically controlled excision may reduce risk. Margin size should probably be determined by tumour thickness [19].

technical aspects

The long axis of the excision should be in the direction of the lymphatic drainage and parallel to the long axis of the limb. This decreases the risk of lymphoedema (especially in the case of subsequent lymph node dissection). Primary closure without dog ears usually requires that the longest axis of an elliptical incision be at least three times longer than the short axis.

Table 1. Clinical trials on surgical margins of radical excision in primary melanoma

Clinical study[a]	Patients (no.)	Thickness (mm)[b]	Margins (cm)	Overall survival (%)	Ref.
French Cooperative Group	336	≤2	2 or 5	87/86 (10-year)	[8]
Swedish Melanoma Group	989	≤2	2 or 5	90/93 (5-year)	[9]
WHO Melanoma Group Trial No. 10	612	≤2	1 or 3	87/87 (10-year)	[10]
Intergroup Melanoma Surgical Trial	486	1–4	2 or 4	80/82 (6-year)	[11, 12]
UK Melanoma Study Group	900	≥2	1 or 3	Not reported; hazard ratio for death was similar in both groups (5-year)	[13]
Swedish Melanoma Trial Group	1000	>2	2 or 4	Final results not reported; preliminary results indicated no differences (5-year)	[14]

[a]Overall survival was not statistically significant.
[b]Breslow.

Table 2. Recommendations for margins of primary melanoma excision based on tumour thickness

Tumour thickness (Breslow)	Recommended definitive margin of excision
In situ	0.5 cm
≤2.0 mm	1.0 cm
>2.0 mm	2.0 cm

Excision should also include subcutaneous tissue down to, but not including, the underlying muscle fascia. The majority of wounds with 1–2 cm margins of excision can be closed primarily. Split skin grafting or local random-pattern flaps are used in a minority of cases. Full-thickness grafts are commonly used on the face or hands for better aesthetic and cosmetic results and may be taken from behind the ear, from the supraclavicular or inguinal region, or from a site of sentinel node biopsy (SNB). Free-tissue transfer with microvascular reconstruction is used mainly for extensive disease on the head and neck. Mohs' micrographic surgery is not appropriate for treating primary melanoma, since the purpose of this is removal of local micrometastases, which, by definition, are discontiguous from the primary lesion. Mohs' surgery may be useful for extensive contiguous disease such as large, clinically ill-defined *in situ* melanoma of the lentigo maligna type, and possibly desmoplastic melanoma.

primary melanoma at specific sites

Melanoma on the palms and soles, nail unit, and head and neck should probably be treated as usual on the basis of tumour thickness. Patients with such lesions have generally been excluded from surgical trials. There are few adequate data on surgical margins and adjuvant chemoradiotherapy for mucosal and anogenital melanoma.

Mucosal and anogenital melanoma. Primary melanoma located on mucosal surfaces represents <3% of all melanoma but is aggressive, with only 20% of patients alive at 5 years [20]. Among mucosal sites, the most frequent are the head and neck (≥50%), female genital tract (mostly vulva, 20%) and anorectal region (∼20%) [20, 21]. The rarest are primary melanomas originating from the urinary tract sites and stomach/bowel. Early detection is unlikely because of the occult anatomic locations.

The diagnosis must be established after a full thickness biopsy of the suspicious lesion with the exception of small lesions suitable for excisional biopsy. Incisional biopsy should include a representative sample from the border of the lesion to help the pathologist in differentiating a primary mucosal melanoma from mucosal melanoma metastasis.

Head and neck mucosal melanoma affects mainly the nasal and oral cavity. The primary approach to treatment of mucosal melanoma is wide surgical resection; however, 5-year OS is only 13–22% [22, 23]. While many cases of mucosal melanoma are treated with surgery alone, radiotherapy or chemotherapy as an adjuvant therapy or even the only modality (radiotherapy) is employed more frequently than in cutaneous melanoma, although the benefit of this is unclear. The most frequent primary site of genital melanoma is the vulva [24]; there is a high incidence of local and distant metastasis. Multiple studies of more than 350 cases of vulvar melanoma indicated that radical vulvectomy (with or without lymphadenectomy) does not improve OS and DFS compared with more limited resection (wide local excision or partial vulvectomy) [25–27]. Radical vulvectomy, in contrast to wide local excision, is associated with very high morbidity and is not recommended. Most cases of melanoma of the penis are treated by amputation [28]. In genital melanoma, staging with SNB may be considered. The majority of melanoma of the anorectal region arises below the dentate line in the squamous mucosa, and so often presents late. No significant differences between abdominoperineal resection and local excision either in OS or DFS have been found [29]. The procedure of choice is a wide local excision with histologically clear margins (ultrasound can be helpful in delineating lesions) that avoids permanent colostomy.

Subungual melanoma. Subungual melanoma accounts for <1% of tertiary referral cases [30]. Amputation of a finger or a toe can only be considered. Distal, function-preserving amputations or even non-amputational approaches are now the usual practice [31].

Melanoma of the face and scalp. For melanoma of the face, normal excision margins may have to be compromised to preserve aesthetic features and functions. There are no data to quantify any adverse outcome of this practice [32]. Melanoma of the ear is treated by wedge excision, or by partial or complete pinnectomy, depending on tumour thickness and patient preference for reconstruction or prosthesis.

Lentigo maligna and lentigo maligna melanoma. Lentigo maligna (LM) is a type of *in-situ* melanoma, and occurs on the head and neck usually in patients >50 years old. Risk of progression to invasive lentigo maligna melanoma (LMM) is well recognised but poorly quantified. Lesions may grow to 5–10 cm or larger. Biopsy is prone to sampling error and may incorrectly indicate benign disease or miss early invasion. Clinical definition may be poor but can be helped by illumination under a Wood's light. The surgical margin required for LM has not been confirmed by any randomised controlled trial: 5 mm or more is usual and gives cure rates of ∼90–95% [33]. A recent retrospective study of 117 cases of LM and LMM treated with a staged, margin-controlled excision technique found that a mean total surgical margin required for excision of LMM was 10.3 mm [33]. However, it is difficult to distinguish between LM melanocytes and atypical melanocytes on sun-exposed skin. Orthovoltage radiotherapy using 7–10 mm margins can give cure rates similar to surgery, but there are fewer data to support this and it is generally only suitable when surgery is not feasible [34].

surgery of regional lymph nodes

sentinel node biopsy

In the last 10 years, the experimental procedure of SNB has been increasingly used. This technique replaced elective lymph node dissection, a method previously recommended for early

treatment of the regional nodal basin despite no effect on OS in several randomised trials (WHO-1 and WHO-14, Mayo Clinical Surgical Trial and Intergroup Melanoma Surgical Trial [35–40]) and significant morbidity. SNB allows identification of the first draining lymph node; if positive for melanoma, subsequent completion lymphadenectomy might improve survival. The Melanoma Selective Lymphadenectomy Trial (MSLT-I) [41] was designed to test this idea. The study confirmed the value of SNB as a staging procedure [42], but failed to detect a difference in survival between patients in the SNB with early lymphadenectomy cohort and those treated later after clinically detected lymph node relapse. However, the 5-year survival rate of a subgroup of patients with intermediate-thickness melanoma (1.2–3.5 mm) (72.3% compared with 52.4%, respectively) did appear to be increased by SNB and early lymphadenectomy. The 5-year survival rate for sentinel node (SN)-negative patients was 90.2 ± 1.3% [41]. An ongoing MSLT-II study is designed to test whether completion lymphadenectomy is required in patients with a positive SNB.

Lymphoscintigraphy and lymphatic mapping is an essential part of the SNB procedure, since lymphatic drainage cannot be accurately predicted [43, 44]. Lymphoscintigraphy provides topographic information about the number of lymph node basin(s) and SN(s). One day or 2–4 h before surgery, dynamic lymphoscintigraphy is performed by intradermal injection of ^{99m}Tc-labelled colloid particles of human serum albumin (as lymphoscint, nanocoll or albu-Res) into both sides of the melanoma excision scar. Different types and doses of labelled solution can be injected; we recommend the use of ^{99m}Tc-labelled colloids with 10–200 nm particles. For trunk, and head and neck, an anterior–posterior view and a lateral view must be obtained to localise all SNs [45]. If only one lymphatic basin is involved in the axilla or groin, SNB may be feasible under local anaesthesia, but in the neck or popliteal fossa, or when multiple basins are involved, it is generally better to operate under general anaesthesia. Following lymphoscintigraphy and 10 min after intradermal injection of Vital Blue dye into the same point(s) as the colloid, the surgical procedure can be conducted. Vital Blue should never be used in the head and neck because of the risk of leaving a permanent tattoo on a visible part of the skin [46], or during pregnancy. During the SNB procedure, a γ-detector probe (γDP) is used to track the radiolabelled tracer towards a single or multiple SNs. This permits a safe, minimal dissection towards the SN. If no vital dye is visible, the γDP should be used immediately after the incision of the superficial fascia in order to reduce the surgical dissection. Devices with intraoperative γ detector in association with intraoperative γ camera have recently reached the market and this way keep confirming that the percentage of SNs detected approaches 100%.

SNB provides accurate staging information, but at present is not known to have any therapeutic value. It is generally used in patients with primary melanomas ≥1.0 mm in thickness, although some investigators question its utility in melanomas thicker than 4 mm. Ulceration, Clark IV and V, mitotic rate per mm^2 and patients choice can also be considered for melanomas <1 mm Breslow thickness.

Histopathology of the sentinel node. The histopathology of the SN is crucial, and the extent of the procedure determines the positivity rate [47–49]. Topography of the SNB metastases [50, 51], and their volume, determine prognosis [52]. Metastases <0.1 mm have only a 2% positivity rate for non-SN on completion lymphadenectomy and the same DFS, distant metastasis-free survival and OS rates as SN-negative patients [52, 53]. However, increasing size of the metastases in the SNB is associated with increasing risk of a positive completion lymphadenectomy and reduced survival.

therapeutic lymph node dissection

The most frequently affected basins are the neck, axilla and groin; involvement of popliteal fossa or epitrochlear lymph nodes is rare. Lymphadenectomy for melanoma has two goals: it may be curative, or it may simply prevent further relapse at that site. Both can only be achieved by meticulous and thorough removal of all involved and at-risk nodes. In general, this means dissection of all five levels of lymph nodes in the neck plus superficial parotidectomy if the primary site is thought to drain to parotid nodes, all three levels in the axilla, and the superficial, deep inguino-femoral and ilio-obturator nodes. Pelvic lymph nodes should always be included if enlarged on preoperative imaging.

Although no convincing data support selective lymphadenectomy, in clinical practice some compromises are sometimes made. For example, when the metastases lie in the posterior triangle nodes (level 5), submandibular (level 1) nodes might be conserved. The ilio-obturator nodes might not be excised unless clinically involved [54], although the greater the burden of superficial inguinal disease the greater the risk of their involvement. Some carry out a frozen section examination of Cloquet's node during the inguinal–femoral dissection; if positive, a deep pelvic dissection is carried out, although a negative Cloquet's node does not guarantee negative pelvic nodes. The dissection of pelvic nodes does not increase long-term post operative complications. These are decisions made on the basis of opinion and experience, and should only be made by melanoma specialists.

surgery of locoregional recurrences

local metastases

The terminology of metastasis between the primary melanoma and draining lymph nodes is confusing, inconsistently defined and unhelpful. In adequately treated primary melanoma, the terms local recurrence, local metastasis, in-transit metastasis and satellite metastasis are all likely to reflect the same biological process of intralymphatic spread beyond the site of therapeutic excision [55]. Since all are characterised by poor prognosis, they should be treated similarly, and are best collectively referred to as in-transit metastases (ITM). It is important to point out that in primary melanoma where adequate surgical treatment has not been carried out, recurrence of melanoma in or adjacent to the scar might represent regrowth of residual primary disease rather than metastasis. In this situation it would be wise to treat the lesion as a thick primary melanoma, since this might offer a chance of cure.

in-transit metastases

Prevention: prophylactic isolated limb perfusion. Early adjuvant treatment of high-risk primary limb melanoma with regional

chemotherapy might effectively treat subclinical ITM and improve survival. Although retrospective studies of isolated limb perfusion (ILP) with melphalan indicated improved outcome in high-risk primary melanoma, a prospective randomised study of wide excision compared with wide excision plus adjuvant ILP in 832 patients [56] did not show any benefit. Rates of progression to systemic metastases and OS were unchanged with only a small improvement in locoregional control.

Treatment of apparent in-transit metastases. Treatment of ITM of the limb depends on their number, site and size [57]. Resectable ITM should be treated surgically with narrow but clear margins. Amputation is not indicated and does not improve survival. With multiple dermal ITM, carbon dioxide laser ablation can be used, but the recurrence rate is very high and this technique is limited to lesions <1 cm in diameter. Other local modalities including radiotherapy, cryotherapy, intralesional injections and electrochemotherapy may be used in specific situations. Regional chemotherapy with ILP or isolated limb infusion (ILI) is the preferred method of treating multiple and frequently recurrent ITM. It treats the whole limb below the point of tourniquet isolation, can achieve 20–50 times higher concentrations of melphalan compared with systemic therapy, and can be performed with minimal locoregional toxicity and minimal systemic leakage [58]. ILP with melphalan can be used in combination with tumour necrosis factor (TNF)-α [59, 60], especially in the case of bulky lesions [60, 61] or after failure of a prior ILP or ILI using melphalan alone [62, 63]. Iliac ILP has the advantage of treating the whole limb up to the groin; ILI only treats to the upper third of the thigh. ILI is probably slightly less effective than ILP, but is less invasive and easier to repeat.

Electrochemotherapy can be indicated for palliation of superficial metastatic lesions when ILP or ILI is not indicated for the general conditions of the patient; a 90% response on the superficial metastases has been reported [64, 65].

surgery of distant metastases

The purpose of treatment of distant metastases is palliation. Surgery is the most effective means of providing this if it is technically feasible, if risk of morbidity and mortality is low and if the patient is likely to live long enough to accrue benefit. A positron emission tomography scan may be used to confirm the finding of computed tomography scanning of a locoregional or distant lesion that is surgically treatable. Good examples are single or localised metastases to the brain, bowel, lung or spinal cord. After careful consideration it may be reasonable to resect a single or localised liver metastasis. Completely resected single distant metastases may occasionally be associated with long survival [66, 67]. More common examples are symptomatic soft-tissue metastases. No prospective study compares surgical with medical approaches to treatment of melanoma patients with a single or very few distant metastases.

radiotherapy

Radiotherapy (RT) is a cancer treatment modality that contributes to the cure or palliation of cancer patients. Cutaneous melanoma has long been considered a relatively radioresistant tumour, due to a distinctly broad shoulder in the low-dose portion of the survival curve [68].

Early studies in melanoma demonstrated that the response rate depended on the size of the dose per fraction; complete response rates were 82% (range 67–92%) for fractions of >4 Gy, but only 36% (range 21–46%) for those of <4 Gy [69–73]. However, recent studies on cell lines show characteristics similar to those of acutely and late-responding normal tissue with a broad variation of intrinsic radiosensitivity [74, 75].

The only randomised study that evaluated the effectiveness of the high-dose-per-fraction irradiation in the treatment of melanoma was planned by the Radiation Therapy Oncology Group (RTOG) in 1983. One hundred and thirty-seven patients without abdominal or brain metastases and with ~50% of the lesions >5 cm were randomised to four fractions of 8 Gy or 20 fractions of 2.5 Gy. In both arms, the overall and complete response rates were 59% and 24%, respectively [76]. Conventional fractionation schedules should be preferred, since they are equally effective in tumour control. In some situations, such as palliation of bone metastases or relief of metastatic lesions in patients with a short life expectancy, a larger dose per fraction is more convenient.

primary melanoma

Surgical resection has proved effective at low risk, so radiotherapy is not a primary treatment for invasive cutaneous melanoma. Radiotherapy should be considered in lentigo maligna, especially in elderly patients with extensive or unresectable disease [33, 69]. It has not been shown to be effective in lentigo maligna melanoma. It may also be used in desmoplastic melanoma, but only when adequate surgical margins are not obtainable [70, 71]. No data support the utility of adjuvant radiotherapy in other forms of cutaneous melanoma. It may rarely be used by melanoma specialists in the presence of positive or close margins where re-resection is difficult to carry out, and local failure could jeopardise the probability of cure.

Radiotherapy can be successfully used in the treatment of mucosal melanoma of the nasal cavity and paranasal sinuses. In contrast to other forms of mucosal melanoma, lesions of the head and neck have the tendency to fail locally before systemic spread, and a radical resection is often difficult to achieve in these regions.

In mucosal melanomas, primary radiotherapy techniques lead to regression rates of 80% [77, 78]. Postoperative radiotherapy looks more efficacious than surgery alone [79, 80], and some authors consider surgery with postoperative radiotherapy a current standard of treatment for malignant mucosal melanoma of the head and neck [81]. However, prospective randomised trials are needed in the adjuvant setting in order to assess the real impact of radiotherapy on local control, quality of life and OS.

regional lymph nodes

The regional recurrence rate after lymph node dissection can be as high as 20–50% [72]. Many factors have been related to an increased risk of regional recurrence including the number of

involved lymph nodes, their size (>3 cm), location (cervical) and the presence of extracapsular extension, which remains the single most important risk factor for relapse. Regional recurrence in the dissected lymph node basin may become unmanageable and can have a serious adverse impact on quality of life and survival. Several phase II studies observed an increase in locoregional control (87–95%) after irradiation with 30–36 Gy in five or six fractions or 50–60 Gy in 25–30 fractions, depending on the site, risk and patient [73, 82–86]. The only published, randomised study, which used 50 Gy in 28 fractions, five fractions/week, found no effect of postoperative radiotherapy on either OS or DFS [87]. The cohort of patients, however, was insufficient to detect small differences in survival and was not stratified for significant prognostic variables. Two recently planned randomised studies [RTOG and the Eastern Cooperative Oncology Group (ECOG)] have been aborted for lack of sufficient accrual, but two other studies, sponsored by the Trans-Tasman Radiation Oncology Group and the Moffitt Cancer Center, are still open and recruiting patients. Although published data remain sparse, American and Australian guidelines recommend postoperative adjunct irradiation in patients with stage III melanoma at high risk of relapse (www.nci.nih.gov, www.health.gov.au, www.nccn.org).

disseminated and recurrent melanoma

Radiotherapy has an important role in the palliation of many symptoms in melanoma patients. A short course of radiotherapy is generally preferred, and good palliation can be obtained in approximately two-thirds of cases; however, the exact degree of the tumour response depends greatly on the tumour size at the time of irradiation [76, 77, 88]. Pain relief and/or decompression in 67% of patients with bone metastases and good palliation in 80–85% of similarly treated patients have been reported using 30 Gy in 10 fractions or 20 Gy in 5 fractions [78, 79, 89]. The overall response rate reported with different fractional doses ranges from 9% to 92%, with a median of 50% [80, 81, 88]. The same percentage was achieved in the RTOG 83-05 randomised study, confirming that radiotherapy represents still the best palliation whenever surgery is not applicable.

brain metastasis

Brain (CNS) metastases affect 10–40% of melanoma patients in clinical studies and represent a sharp decrease in quality of life and survival. CNS is the first site of recurrence in 15–20% of patients with stage IV melanoma. In the majority of patients with multiple lesions, surgery is rarely indicated, and chemotherapy alone is largely ineffective [90]. The median survival in untreated patients has been reported to be as low as 1 month [91], and despite early detection of frequently asymptomatic metastatic disease using conventional imaging modalities, the prognosis remains poor with reported median survival ranging from 2 to 8 months.

Multiple brain metastases. The median survival of symptomatic patients with multiple brain lesions treated with anti-oedema therapy (corticosteroids and osmotic diuretics) is only 2 months and can be extended to 4–6 months after whole-brain radiation therapy (WBRT). With both treatments, 60–70% of patients experience improvement in neurological symptoms and performance status with no significant differences between various conventional fractionation schemes (20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions) [92]; however, the procedure is not without morbidity (hair loss, brain oedema, lethargy, cognitive impairment).

Single or few brain metastases. Treatment options for patients with just one or a few, smaller brain metastases include neurosurgical resection and stereotactic irradiation. The feasibility of resection depends on the lesions' number, size and location, neurologic symptoms and deficits, and also on the presence of extracranial disease, age and performance status. Patients with multiple, but resectable brain lesions may have a prognosis similar to that of patients with solitary brain lesions [93] and may benefit from surgical resection of a symptomatic or life-threatening brain lesion [94]. Surgery followed by WBRT improved survival compared with WBRT alone [95, 96].

Stereotactic radiosurgery (SRS) is a highly effective local treatment of brain metastases that provides targeted high-dose irradiation of one to six lesions with a diameter not exceeding 3–4 cm, in a single or multiple sessions [97]. Recent publications indicate that its efficacy using either multiple cobalt sources (gamma-knife) or a linear accelerator (Linac) is similar to that of surgical resection. The reported local control rates from uncontrolled studies range from 80% to 96% with a median survival in the range 7–12 months; however, in patients with multiple lesions, median survival decreases to 4 months [98]. Adjuvant WBRT was found to decrease the distant brain failure in SRS-treated patients from 64% to 17% after 6 months [99].

conflict of interest disclosures

The authors declare no conflict of interest.

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