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MELANOMA (RJ SULLIVAN, SECTION EDITOR)

Primary Melanoma: from History to Actual Debates

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Abstract

Purpose of Review This review describes the long scientific background followed to design guidelines and everyday clinical practice applied to melanoma patients. Surgery is the first option to cure melanoma patients (PTS) at initial diagnosis, since primary cutaneous lesions are usually easily resectable. An excisional biopsy of the lesion, with minimal clear margins, can be obtained in the vast majority of cases. Punch biopsies may be proposed only in case of large lesions located on specific cosmetic or functional areas like the face, extremities, or genitals where a mutilating complete resection would not be performed without prior histological diagnosis.

Recent Findings After the histologic confirmation of melanoma, definite surgical excision of the scar and surrounding tissue is planned, to obtain microsatellite free margins. The width of these margins has been identified following the results of several clinical trials and it is either 1 or 2 cm, depending on the Breslow thickness of the primary tumor. Following the latest staging system proposed by the American Joint Cancer commission (AJCC), a sentinel node biopsy (SNB) is usually performed in case of a primary lesion > 0.8 mm thickness or for high-risk thinner lesions, if no evidence of nodal involvement has been identified clinically or radiographically.

Summary Surgical management of primary melanoma is well established. There is debate on the optimal surgical margins for 1–2 mm melanomas. There are specific considerations for special primaries (bulky, extremity, mucosal). Sentinel node (SN) evaluation does not improve survival, but is routinely used as staging.

Keywords Melanoma · Surgery · Excisional margins · Sentinel node biopsy · Lymph node dissection

Introduction

Surgery is a highly effective therapy for melanoma, but its indication is becoming more and more restricted to early stages. This paper will go through the classic surgical indications and surgical technical procedures for the different clinical presentations for primary disease up to the indication for sentinel node diagnosis.

This article is part of the Topical Collection on *Melanoma*

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Primary Melanoma: from an Incurable Disease to One of the Most Curable Cancers

In the first scientific paper dedicated to surgical margins around a primary melanoma from the early 1900s, pathologist Dr. Handley suggested to remove 5 cm of skin around a primary melanoma [1]. Since then, clinical practice and guidelines have become much more conservative. The rational for 5 cm margins was based on his everyday post mortem autopsy practice, as the presence of satellites could extend up to 5 cm surrounding the primary melanoma, due to late diagnosis. Thanks to the WHO project in the early 1960s coordinated by Veronesi and Cascinelli, the natural history of melanoma patients has dramatically changed. Due to educational programs around the world, the concept of early recognition and excision followed by histological diagnosis of every suspicious mole permitted that primary melanoma became one of the most curable cancers. Since then, most studies were dedicated to reduce the enormous quantity of healthy skin removed around a primary lesion, as in each excision a demolition up to 5 cm of healthy skin required major plastic surgery repair.

Modern treatment of cutaneous primary melanoma is usually characterized by two-fold cutaneous resection: the initial procedure is the tumor excisional biopsy including some initial layers of subcutaneous fat to reach a complete histological evaluation of the lesion. Two important histological factors of the primary that help indicate the prognosis in terms of chance of involved lymph nodes and disease-free and melanoma-specific survival are the primary Breslow thickness and presence of ulceration [2•]. Mitotic rate as a continuous variable also helps indicate the prognosis further, but due to the large inter-observer variability for the assessment, it was abandoned as factor in the use for primary melanoma staging by the American Joint Committee on Cancer (AJCC).

The golden standard for histologic confirmation of primary melanoma is excisional biopsy. Shave excision should not be applied, since this compromises the histologic evaluation. Also Mohs surgery and punch biopsies are not recommended, but may be used in defined situations. For example, large primary lesions on the face, on genitals, or on extremities where there is an immediate surgical excision of the whole primary lesion would require a delicate plastic surgical repair.

The second and definitive surgical excision is planned around the scar of a previous excisional biopsy en bloc with apparently healthy cutaneous and subcutaneous margins down to the muscle sheath, which is normally conserved as there is no evidence of a benefit from removing it and is planned simultaneously to a sentinel node biopsy (SNB) if indicated [3–8].

Most (inter)national guidelines on resection margins are based on the results of six prospective randomized trials that have evaluated the effect of excision margins width around the primary lesion on patients' survival and melanoma recurrences. Three trials have selected patients with melanomas thinner than 2 mm: the French Cooperative Group Trial, the first Swedish Melanoma Group Study, and the World Health Organization (WHO) Melanoma Program Trial 10. The French trial and the Swedish trial accrued patients with less than 2-mm thick melanomas and confirmed that an excision with 2-cm margins is safe in comparison to traditionally used wide excisions with 5-cm margins. The French trial (300 PTS) showed 10-year disease-free survival rates (DFS) of 85% and 83% respectively and overall survival (OS) rates of 87% and 86% for the 2-cm margin and 5-cm margin groups. The long-term follow-up results of the Swedish trial (989 PTS) similarly showed no significant difference with respect to recurrence-free or OS between the groups. The WHO trial (612 patients) compared less than 2-mm thick melanomas excised with at least 3-cm margins with those excised with 1-cm margins. This trial did not show any differences in OS and DFS between the two groups and no patient with a primary tumor thinner than 1 mm developed local recurrence after excision of the tumor with a 1 cm margin. The Intergroup Melanoma Surgical Trial conducted by Balch et al. randomized 486 melanoma patients of intermediate thickness (1–4 mm), in two groups of 2-cm versus 4-cm final margins. The authors reported no difference between the narrow and wide excision groups for local recurrences (2.1% vs. 2.6%, respectively) and for OS (79% vs. 81%, respectively), but primary closure was possible in 89% of patients with narrow margins, versus 54% in the wide margins group ($p < 0.001$).

The long term follow-up results (> 19 years median Follow up) of the second Swedish trial (Scandinavian-Baltic trial, 936 PTS, > 2 mm Breslow, 2 vs 4 cm margins) similarly showed no significant difference with respect to recurrence-free or OS between the groups.

For patients with melanoma thickness above 4 mm, the recommendations can be based on results from one non-randomized and two randomized studies. First, in a non-randomized study, Heaton et al. showed that excisions with margins wider than 2 cm have no impact on the local recurrence rates, DFS, and OS. In a prospective, randomized study by the UK Melanoma Study Group and the British Association of Plastic Surgeons, 900 patients with at least 2-mm thick primary tumors were randomized to narrow or wide excision margins of 1 cm or 3 cm, respectively. Most patients did not receive a SNB and the distribution of this diagnostic procedure in the 2 arms is not equal. Differently to all other studies, the UK trial reported 194 deaths to melanoma in the 1 cm group compared with 165 in the 3 cm group (unadjusted hazard ratio [HR] 1·24 [95% CI 1·01–1·53]; $p = 0·041$). This could be an effect of the different distribution on SNB vs no SNB patients in the 2 groups with more PTS in the 1 cm group presenting N+, creating a bias on the survival which is N+ driven and not linked to the surgical margins of 1 vs 3 cm. Although a higher number of deaths overall occurred in the 1 cm group compared with the 3 cm group (253 vs 241), the difference was not significant (unadjusted HR 1·14 [95% CI 0·96–1·36]; $p = 0·14$). A slightly higher rate of local recurrences was noted in the group with the narrow margin (hazard ratio of the local recurrence rate for the 1-cm margin was 1.26, $p = 0.05$). From both patient quality of life and hospital management considerations, two thirds of patients with the 3-cm margin of excision had the procedure done under general anesthesia in contrast to what performed in only one third of patients with the 1-cm margin of excision ($p < 0.001$). Since the risk of death from melanoma and locoregional recurrences in this trial were higher in the 1-cm than 3-cm group, authors recommended margins of excision wider than 1 cm for melanomas thicker than 2 mm. In conclusion, the possibility of universal recommendations for all melanoma thicker than 2 mm was suggested by results from the earlier mentioned Scandinavian-Baltic trial. The study indicated no differences in outcomes of the treatment between the two study arms [9–21, 22••, 23–28].

A meta-analysis has been performed of the 6 previously discussed trials examining different wide local excision margins. This meta-analysis concluded that although OS, relapse free

survival and locoregional recurrence were not significantly affected by narrow margins, the narrow margins did lead to a worse outcome for melanoma specific survival and might not be safe.

However, this meta-analysis was criticized for a number of things. First, 3 of the 6 studies did not include information on ulceration status, an important prognostic factor for melanoma outcome. Secondly, the meta-analysis was driven largely by the UK study, which did not require routine SNB staging, which could influence the number of N+ disease in the narrow arm, leading to a detrimental outcome, rather than it being the effect of a narrow margin. Finally, it seems odd that OS, RFS, and locoregional recurrence were all not significantly impacted, only MSS was worse, which might simply be due to a reporting bias rather than a true effect [29•].

Concluding, meta-analyses of these trials do not reveal statistically significant differences in terms of mortality or local recurrence according to the width of surgical margins proposed. National and international discussions on this topic have defined the following indications based on the different thickness of primary melanomas: melanoma in situ, 0.5 cm; melanoma < 1 mm, 1 cm; melanoma 1–2 mm, 1–2 cm; melanoma 2–4 mm, 2 cm; melanoma > 4 mm, 2 cm [25–28, 29•, 30–38]. Data about 1- to 2-mm thick invasive melanoma are inconclusive. However, many national guidelines suggest that a 1-cm margin may be sufficient. The only exception to the abovementioned margins is for specific anatomical locations such as the face, where much narrower margins can be maintained to avoid excessive damage.

T2–T4 melanomas are subject to wide local excision with 2–3 cm margins, but based on the previous randomized controlled (RCT) trials, it is unsure if a 1 or 2 cm margin is sufficient and safe for such disease, as 95% might be able to achieve local control. The MelMarT study is an ongoing phase 3 RCT addressing this issue. Already the pilot phase of the study with 400 patients has been completed, and the initial results demonstrated that the 2 cm group required more reconstructions than the 1 cm group (34.9% vs. 13.6%). There was also more wound necrosis in the 2 cm group (3.06% vs. 0.5%). This did not show a negative impact on quality of life (QoL) assessments at 12 months postoperative. Efforts are underway to accrue 2998 patients into the MelMarT study (NCT NCT03860883): in this study, the primary endpoint is local recurrence and the secondary endpoint is Melanoma Specific Survival.

The rational for 5 cm margins was based on prof Handley's everyday post mortem autopsy practice, as the presence of satellites around a primary melanoma could only usually be eradicated if a 5-cm large margin would have been planned in front of the typical late diagnosis of primary melanomas at that times. Behind this situation of late diagnosis, a usual common sense was telling "not to remove any mole, as the removal itself could be the cause of a rapid disease progression and death of a patient." At the primordia of surgical oncology, moles were removed either surgically or with a shaving or diathermy approach and not examined because the diagnostic culture on primary melanoma was completely different and lesions less than 2–3 cm even if ulcerated were removed or burnt with diathermy coagulation but not sent to the pathologist as not suspected to be potentially malignant: several of these lesions progressed to a metastatic situation and bearing in mind the previous excision of a mole, the oncological justification was correlated to that earlier episode. Only after the WHO melanoma group activated the first cooperative international project dedicated to early diagnosis of primary melanomas during the 1960s, it appeared very clear that surgery would never be the cause of a fatal progression of a cancer like melanoma, but that only an early diagnosis could save the patients from a fatal disease progression regardless to any surgical procedure proposed whenever the initial diagnosis was done. In 4 years, we can now confirm that thanks to the project coordinated by Veronesi and Cascinelli within the WHO, the natural history of melanoma patients has dramatically changed: from an incurable disease, thanks to the proliferation and fertilization of educational programs around the world, the concept of early recognition and excision followed by histological diagnosis of each, even unsuspicious, mole, permitted that melanoma became one of the most curable cancers. Up to now, a single surgical procedure in front of a clinically evident primary melanoma is not routinely proposed, mainly due to the uncertainty of Breslow thickness. Different techniques have been proposed to preoperatively study the correct thickness of primary melanoma, from ultrasound to epiluminescence microscopy, but none has been really been clinically adopted to drive for the final margin of excision directly at the initial surgical procedure [30–40].

Primary Melanoma on the Extremities

Melanoma arising in a specific body area requires individualization of the best surgical approach which may be more clinically challenging and modified to adapt to anatomic or cosmetic specifics of the patient.

Fingers and toes can be affected by primary melanomas and represent a typical exemplification of this concept. During the last decades, a more conservative philosophy has reached a global consensus and when feasible, a simple cutaneous excision can be proposed as successfully as in contrast to important anatomical finger or toe demolitions. Conditio sine qua non, the underneath bone needs to be clear from invasion of the neoplasm, which is the case in the majority of melanomas. Subungual melanoma accounts for less than 1% of entries in the databases of tertiary referral centers. One of the major problems is the case of a delayed diagnosis that leads to presentation at a more advanced stage [41–44].

Bulky primary lesions can sometimes be diagnosed on extremities. If an amputation would seriously compromise the quality of life and when such an aggressive surgical procedure could be eventually proposed only in second line, alternative

approaches can be proposed within the concept of an integrated surgical locoregional procedure, but no bone involvement should be documented. The 2 most common procedures are an isolated limb perfusion (ILP) or an electrochemotherapy (ECT) treatment [45, 46, 47•, 48]. New approaches to bulky lesions consist of systemic therapy with combination BRAF/MEK inhibitors in case of a BRAF mutation. These have high response rates and can quickly reduce tumor burden, but are only available for circa 50% of melanoma patients in which the melanoma harbors the BRAF mutation.

Immunotherapy can also downstage bulky tumors, but due to the lower chance of response it is less ideal as induction therapy to achieve a quick and significant reduction. Oncolytic virus treatment is a last new option to treat bulky disease. Talimogene laherparepvec (TVEC) is a first FDA/EMA approved oncolytic virus for melanoma. Recent institutional studies have shown even higher response rates than in the phase 3 registration study, especially when used for earlier stages of disease [49–53, 54•, 55, 56, 57•, 58, 59].

Opposite from the concept of bulky inoperable primaries, to decrease locoregional recurrences after surgical treatment of high-risk primary melanoma in the limbs, prophylactic isolated limb perfusion (ILP) with melphalan has been proposed. A large, prospective randomized study with 832 patients did not suggest any benefit of prophylactic ILP on progression to systemic metastases or on OS and demonstrated only an improvement of locoregional control. Since the procedure is costly and accompanied by considerable morbidity, prophylactic ILP cannot be recommended as adjuvant therapy after surgical excision of high-risk primary melanoma [60, 61].

Head and Neck Melanoma

Lentigo maligna/melanoma is a peculiar histotype of the face and scalp regions as a consequence of chronic sun exposure and usually affects elderly people. The role of Mohs micrographic surgery is controversial and generally not recommended for these lesions, where at least a 0.5 cm surgical margin should be always reached. The hypothetical risk of cutting parts of melanoma in the attempt to excise a clear margin during Mohs surgery is the reason why this technique is not accepted by most oncology centers. However, this technique modified in a concept of intraoperative frozen section for histologic evaluation of the margins may have a role in the management of melanoma at anatomic sites where standard margins may be difficult to be clearly detected [62–70].

Radiotherapy should be indicated only for palliative reasons in non-operable patients for local control of the disease [71, 72].

Some primary tumor features other than thickness or ulceration have been discussed as important factors and should be taken into account in decisions about final excision margins. As an example, wider margins have been recommended for desmoplastic melanoma. No randomized trial is of support to such an indication [73].

Melanoma of Mucosal Surfaces

Primary melanoma located on mucosal surfaces is a very rare disease that represents less than 3% of all melanoma and has biologically aggressive behavior. Among mucosal sites, the most frequent are head and neck mucosal membranes (more than 50%), female genital tract (mostly vulva; approximately 20%), and anorectal region (approximately 20%). The rarest are primary melanomas originating from the urinary tract sites and stomach/bowel. Early detection is difficult for these tumors because of the occult anatomic locations. Whereas the general 5-year relative survival of cutaneous melanoma was 86%, that of ocular 74% (67–81%), vulvar 40% (31–49%), and anorectal 15% (8–22%) in a population study from the Netherlands.

The diagnosis can be established through a full thickness biopsy of the most suspicious area of a lesion; this step can be avoided in case of small lesions suitable for excisional biopsy. The general therapeutic consensus is to attempt a complete surgical excision of the primary site with clear margins eventually followed by postoperative radiation therapy for microscopic or macroscopic residual disease.

Head and neck mucosal melanoma affects mainly the nasal and oral cavity. The primary approach to treatment of mucosal melanoma is a wide surgical resection; however the 5-year OS remains in the range of 13–22%. A study by Meleti et al. demonstrated that surgery + radiotherapy seemed to be superior for local control and survival for head and neck mucosal melanoma compared to surgery alone. This observation was seen across other studies as well [74–76, 77•, 78, 79–82].

The most frequent primary site of genital melanoma is vulva. Multiple studies of more than 350 cases of vulvar melanoma suggested that radical vulvectomy (with or without inguinofemoral lymphadenectomy) does not improve overall and disease-free survival compared to more limited resections (wide local excision or partial vulvectomy with adequate tumor-free margins). Radical vulvectomy, in contrast to wide local excision, is associated with high morbidity.

Most cases of melanoma of the penis have reported amputation of the organ. More recently, a conservative approach is followed whenever feasible similarly to melanoma of the extremities [83–92].

The majority of melanoma of the anorectal region arises below the dentate line in the squamous mucosa. The mortality rate is high and no significant differences between abdominoperineal resection and local excision both in DFS and OS have been found; consequently, most studies suggest that extended surgical procedures add little value. The

procedure of choice is a wide excision with clear margins (ultrasound can be helpful in delineating lesions extension) that avoids permanent colostomy. Abdominoperineal resection should be attempted only for large primary tumors not amenable for local excision without documented distant dissemination [93–96].

In genitals and mucosae melanomas, staging procedure with sentinel node biopsy should be considered as described later for cutaneous melanoma.

Ocular melanoma is generally managed by ophthalmologists and will not be discussed on this article [97].

Recent developments of systemic therapy for cutaneous melanoma have not been verified for mucosal melanoma. First, the activating BRAF mutation is rarely found for mucosal melanoma, meaning that BRAF directed therapy is therefore usually not an option. At the same time, the response rates for mucosal melanoma for immune checkpoint blockade (ICB) seem to be much lower than for cutaneous melanoma. In a study with anti-PD-1 or combined anti-PD-1 with anti-CTLA-4, the overall response rate (ORR) was ORR 23.3% (14.8–33.6%). Thus, this does not seem a viable option for most cases, but could be considered for locally advanced, bulky disease [76, 77•, 78].

Surgical Technique Issues Towards the Definitive Excision

From the surgical point of view, a pigmented lesion suspicious to be a primary melanoma should be excised as early as possible by a limited margin of 1–2 mm which completely includes the lesion; incisional biopsies are accepted only in case of large lentigo maligna melanoma of the face or mucosal melanosis to reach a confirmation of the diagnosis. To obtain a correct histological evaluation, it is important to include in the specimen of an incisional biopsy a limited amount of the most suspicious part of the mole and if possible some normal skin.

The radical treatment of primary melanoma can be divided into two main elements: margins and orientation of the definitive excision and reconstruction of the defect. The margins of the definitive excision should be measured in each direction from the periphery of the lesion or scar. The long axis of the incision should be in the direction of the lymphatic drainage and parallel to the long axis if on limbs, unless the primary excision is perpendicular to that hypothetical axis where the re-excision should follow the same line; this decreases the level of peripheral edema (especially in the limbs in case of subsequent potential need for lymph node dissection). Primary closure usually requires the longest axis of an elliptical incision to be at least 3 times longer than the short axis. Excision should include also subcutaneous tissue down to, but not including, the underlying fascia. The majority of wounds after 1- to 2-cm margins of excision can be closed by primary sutures. Skin flaps are used to alleviate tension and to permit approximation of wound borders. In a minority of cases, when the wound cannot be closed primarily, more complex reconstructive techniques, such as skin grafting and the use of local and distant flaps, are employed. To minimize the risk of local recurrences, it is recommended to use free skin grafts from the contralateral side. Full thickness grafts are commonly used on face or hands for better esthetic and cosmetic results and may be taken from behind the ear, from the supraclavicular region, or from any glabrate area not at close risk of in transit metastatic seeding [98–101, 102•].

Sentinel Lymph Node Biopsy

Several different methods for intraoperative lymphatic mapping have been reported: from Blue staining by Donald Morton in 1992 (sensitivity 69–92%) to the currently used combination of lymphatic scintigraphy and use of an intraoperative radionuclide probe with eventually an intraoperative gamma camera. The SOLISM study in Italy examined 1300 patients with Breslow thicknesses > 1 mm or Clark levels > IV and contributed to standardize the procedure for lymphatic scintigraphy, use of vital dye and surgical technique, among other methodological and prognostic aspects [103].

It is difficult to demonstrate a prognostic statistical benefit for any specific surgical procedure on melanoma patients. In the MSLT I trial, patients underwent either clinical monitoring of lymph nodes or SNB after primary tumor excision. This study confirmed the high accuracy on identification of SN and even if it showed that it is the most significant prognostic factor for melanoma patients independently from the characteristics of the primary tumor, there was no demonstration of any survival benefit.

Currently SN biopsy is performed in patients with Breslow thicknesses ≥ 0.8 mm with associated histopathology, or with Breslow thicknesses < 0.8 mm, but with ulceration; Mitotic rate and Clark levels, specifically in case of levels IV or V, are no more considered of prognostic significance in the latest AJCC 8th classification [104–138].

Ultrasound (u.s.) has been widely used in the preoperative evaluation of nodal basins in melanoma patients. Only few experts can be identified worldwide with adequate experience in detecting minimal deposits in the locoregional nodes during patients staging. Christian Voit left to our community an immense repertoire of knowledge and her premature death will always be remembered: she was a pioneer in defining the parameters that should be followed by ultrasonographists analyzing nodes. Her results cannot be replicated on large scale as has been demonstrated by the US results during the MSLT II study where the poor identification of metastases as compared to the academically programmed ones led to a precocious abandon of u.s. within the preoperative exams to perform before accruing patient in the study [139–145].

Role of Pathologists on Primary Melanoma and SNB

The role of pathologists is crucial in the prognostic staging of primary lesions and SN.

Microsatellites even though described by pathologists for decades have been included in the AJCC 8th classification and bear an important prognostic and biologic role. This parameter should always be addressed in a histologic report. The confirmed presence of microsatellites virtually brings a patient to stage III implicating that a SNB could potentially be avoided. At the moment, no adjuvant therapy has been indicated to patients only on the basis of this parameter, but new studies will possibly be able to evaluate the necessity of such an approach.

Different, but probably not less important, appears the description of mitosis: this parameter was included in the AJCC 6th and 7th classifications but was then excluded from the 8th edition. Originally mitoses were numbered on the histological fields that each microscope in different ways was analyzing: each microscope had different magnification of the histological slides, so it was impossible to compare any data as the origin of the method was different between all observers. Since pathologists agreed to measure mitosis on the basis of square millimeters, this parameter seemed to become reproducible and comparable between worldwide observers. It appeared as an important decision taken by the AJCC melanoma commission to exclude this parameter again after years of routine use (SNB was indicated on < 1 mm melanoma patients if ≥ 1 mitoses were present) based on the difficulty to standardize the count of mitosis by pathologists. Nevertheless, mitoses as continuous variable are prognostic for survival [3].

SN histopathology is a crucial step in the staging of melanoma patients. Different approaches have been proposed from extensive to minimal methods where the basic concept on which there is universal agreement is that the more of a SN is processed and sectioned, the higher % of positivity is detected. This stated, there is no similarity in the procedure to analyze a SN in different macro areas of the world: Europe has generally adopted the European Organization of Research and Treatment of Cancer (EORTC) Melanoma Group approach, while USA and Australia perform less extensive and different from each other sectioning protocols. The comparison of results from histopathology on SN in different environments worldwide appears to be not scientifically accurate on this basis [146–150, 151••].

Conclusions

Surgical management of primary melanoma is a well-established approach with minor possibilities to perform mistakes when standard surgical guide lines are followed. This phase can be usually managed by a collaboration between dermatologists and surgeons and will be concluded by dedicated melanoma surgeons through the SNB procedure, where nearly 80% of patients will come to a more favorable diagnosis of negative metastatic spread to locoregional nodes. The role of pathologists is strategic to reach an accurate staging of early diagnosed melanoma patients. SNB did not show any survival benefit based on the results of MSLT I study, but this seems a common place within all surgical trials on melanoma history and does not reduce the fundamental role of this procedure in the staging and early detection of metastatic spread on melanoma patients. By far, the most important project that modified the natural history of melanoma patients was conducted by the WHO melanoma program headed by Veronesi and Cascinelli, who, from an incurable disease, turned melanoma into a disease with a more favorable prognosis, indeed curative in more than 80% of patients. This was obtained based "only" on educational programs throughout the world during the late 1960s of last century.

There is still some debate on the optimal surgical margins for 1–2 mm melanomas. There are specific considerations for special primaries (bulky, extremity, mucosal). Sentinel node (SN) does not improve survival, but is routinely used as staging.

Compliance with Ethical Standards

Conflict of Interest Alessandro A.E. Testori declares that he has no conflict of interest.

Stephanie A. Blankenstein declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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