Surgical Treatment of Melanoma: A Survey of Italian Hospitals

Alessandro Testori a, Vanna Chiarion-Sileni b, Ignazio Stanganelli c, Carlo Riccardo Rossi d, Franco Di Filippo e, Ruggero Ridolfi f, Giorgio Parmiani g, Sara Gandini a, Javier Soteldo a

aIstituto Europeo di Oncologia, Milan, bMedical Oncology Unit 2, Veneto Institute of Oncology, IRCCS, Padua, cScientific Institute of Romagna for the Study and Treatment of Tumors, Meldola, dGeneral Surgery Clinic, Department of Oncological and Surgical Sciences, University of Padua, Padua, eGeneral Surgery, National Cancer Institute Regina Elena IRCCS, Rome, fImmunotherapy Unit, Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, and gUnit of Immuno-Biotherapy of Melanoma and Solid Tumors, San Raffaele Foundation Scientific Institute, Milan, Italy

Introduction

Surgery is the only effective therapy for melanoma, but its usefulness is mainly limited to early stages. Treatment of primary melanoma consists of excision of the tumor or surgical scar of a previous 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 [1–6]. Current guidelines on resection margins are based on the results of randomized trials: WHO Melanoma Trial No. 10 [7], Intergroup Melanoma Trial [8], Swedish MSG Trial [9], European Trial [10] and UK Trial [11]. All of these had two arms, one with patients treated with narrow resection margins and one with wider margins. All patients had histologically confirmed melanoma and did not have invasive disease at staging. Meta-analyses of these trials do not reveal statistically significant differences in terms of mortality or local recurrence according to the width of resection margins [12–14]. Therefore, integrating the data emerging from these trials, the following margins are recommended: (1) melanoma · surgery · incision margins · lymph node biopsy

Key Words

Melanoma · surgery · incision margins · lymph node biopsy

Abstract

Surgery is the first option for treating melanoma regardless of stage at presentation. We surveyed a representative sample of hospitals to evaluate management and quality of surgical indications for melanoma in Italy. At analysis, hospitals were grouped into high- or low-volume centers, with the population median of 25 diagnoses serving as the cut-off. Surgery for primary melanoma was similar between hospital groups. More high-volume centers were organized to perform sentinel node biopsy (91 vs. 56%). There were no major differences between high- and low-volume centers concerning the surgical approach to stage III and IV disease.
ma in situ: 0.5 cm; (2) melanoma <1 mm: 1 cm; (3) melano-
ma 1–2 mm: 1 cm; (4) melanoma 2–4 mm: 2 cm; (5)
 melanoma >4 mm: 2 cm. The only exception is for particu-
lar anatomical locations such as the face, where much nar-
rrower margins can be maintained to avoid excessive dam-
age. Moreover, in the case of lentigo maligna, definite histol-
ogical confirmation of clean margins is of fundamental
importance, since the resection margins are very narrow.

Sentinel Lymph Node Biopsy

on a method for intra-operative lymphatic mapping with
Patent Blue staining, which has a reported sensitivity of
69–92%. Sensitivity can be improved to nearly 100% by
identifying the drainage basin pre-operatively with lym-
phatic scintigraphy and using an intra-operative radionu-
diode probe to identify the sentinel lymph node (SLN). Nu-
merous studies have investigated the best procedure for
and biological significance of SLN biopsy in melanoma.

In the MSLT-I trial patients had primary tumors ex-
cised and then underwent either clinical monitoring of
lymph nodes or SLN biopsy. Although the results con-
ﬁrmed the high sensitivity of SLN biopsy and showed that
it is the most significant prognostic factor, there was no
survival beneﬁt [16].

The SOLISM study examined 1,300 patients with
Breslow thicknesses >1 mm or Clark levels >IV and con-
tributed to standardizing procedures for lymphatic scin-
tigraphy, the use of vital dyes and surgical techniques,
among other aspects [17].

Currently SLN biopsy is performed in patients with
Breslow thicknesses ≥1 mm with associated histopathol-
ogy, or with Breslow thicknesses <1 mm, but with ulcer-
ation or high mitotic indexes; Clark levels (speciﬁcally
in case of IV or V) are no more considered of prog-
nostic signiﬁcance in the last AJCC classiﬁcation. Gen-
erally, centers not participating in the MSLT-II trial
(NCT00297895) follow the consolidated guidelines: pa-
tients with negative SLN are monitored with clinical fol-
low-up, while SLN-positive patients, including those with
micrometastases, are subjected to complete lymph node
dissection.

Lymph Node Dissection (Axillary, Inguinal-Iliac-
Obturator, Popliteal, Epitrochlear)

According to the surgical guidelines lymph node dis-
section should be performed with a positive SLN result or
documented lymphatic metastasis; the extension of lymph
node metastases has not been universally accepted in all
the basins frequently involved in dissection areas [18, 19].

Metastases in Transit

Melanomas that spread in the lymphatic system and
develop lesions in the soft tissue before reaching a locore-
gional lymph node are known as in transit metastases.
These may take the form of cutaneous or subcutaneous
metastases. Surgery is indicated if there is/are only one/few
metastatic lesion/s. If metastases are numerous or recur
rapidly after removal and are located in the limbs, hyper-
thermic isolated limb perfusion (ILP) is administered to
cause tumor regression. Electrochemotherapy (ECT) is a
new treatment modality for cutaneous and subcutaneous
metastases of numerous tumors, including melanoma. ECT
increases antitumoral efﬁcacy by combining a che-
motherapeutic with electroporation, which increases cell
membrane permeability and hence drug uptake [20–23].

Distant Metastases

Stage IV metastatic melanoma, as for other tumors, is
the phase of the disease with distant metastases. The me-
tastases occur most frequently to the liver, lung, brain,
small bowel and bones. Unfortunately, survival in this
stage of the disease is very low, with a mean overall sur-
vival of a few months.

Methods

Briefly, a nationwide survey of clinicians responsible for the di-
agnosis, therapy or follow-up phases of melanoma care in Italian
hospitals was conducted. Italian hospitals with ≥200 beds (n = 285)
were subdivided into 145 hospitals with 200–399 beds and 140 hos-
pitals with ≥400 beds and a proportionally stratified random sam-
pel (n = 120 centers), stratified by number of beds and geographic
distribution, was selected. Two or three clinicians were interviewed
at each center, resulting in approximately 250 interviews and a pre-
dicted margin of error – 95% conﬁdence level – of 7.7%.

Based on the ﬁndings, centers were grouped by number of new
melanoma diagnoses per year into low- and high-volume centers,
around the median value of 25. Variables were analyzed in the to-
tal sample/total Italian hospitals, and comparisons were made be-
tween high- and low-volume centers using Pearson’s χ² test and
the zeta test at 95% conﬁdence level. Detailed methods are pre-
sented elsewhere in this supplement [24].

Results

Primary Melanoma

Our data show that the indications from clinical trials
are being followed in both high- and low-volume centers;
margins are based on Breslow thickness. There were no
major differences among Italian hospitals regarding re-
section margins.
Sentinel Lymph Node Biopsy

There were several important differences between the high- and low-volume centers regarding SLN biopsy: while 91% of high-volume centers use SLN biopsy, it is used in only 56% of low-volume centers (p < 0.001). Among centers that do not perform SLN biopsies, all of the high-volume centers have agreements with referral centers for this service, while only 81% of low-volume centers do, meaning that in nearly one fifth of the low-volume centers, patients must find adequate care on their own.

Regarding biopsy methods, a majority of high-volume centers use the Gamma Probe with Patent Blue dye (69%), while in low-volume centers the Gamma Probe is used somewhat more often without Patent Blue (79%). Concerning the Breslow thickness cut-off for indicating SLN biopsy, the results are the same for melanomas between 1 and 4 mm (85%) and statistically different in those >4 mm, where they are performed in more of the low-volume centers (92 vs. 79%, p = 0.006). For Breslow values <1 mm the results were similar in both groups, with the exception of Clark levels IV/V, which triggered biopsy in 71% of high-volume centers and 49% of low-volume centers (p = 0.01). Results were similar between groups for indications in case of regression (79%), or patient selection (15%), remaining low for both ulcerated (46%) and nodular (54%) melanomas.

When a primary melanoma is located between the zygomatic arch and the mastoid, 91% of high-volume centers perform SLN biopsy, compared to 56% of low-volume centers (p < 0.001). The type of intervention is similar (superficial parotidectomy) and is mainly performed when there is documented metastasis.

Stage III Disease

Results were similar in both groups. Axillary dissection on three levels is performed for macrometastases in 80% of centers and for micrometastases in 65%. When IHC/PCR is positive, all three levels are dissected in 40% of cases. Regarding the neck area, whether macro-/micrometastases or IHC/PCR-positive cases are present, radical dissection or modified radical dissection is performed, with no difference in the procedures. Regarding the inguinal-iliac-obturator nodes, the only significant difference between groups was when Cloquet’s node is positive for micrometastases, in which case inguinal-iliac-obturator dissection was performed more frequently in low-volume centers (59 vs. 37%, p = 0.01). All other conditions were similar between groups.

Stage IV Disease

In these cases both high- and low-volume centers are in agreement in treating single visceral and small superficial metastases with surgery. High-volume centers were more likely to use palliative surgery (p = 0.001).

Discussion

Our analysis of surgical approaches to melanoma treatment in Italian hospitals did not reveal major differences between high- and low-volume centers. The most important differences were in the organization of specific treatments that require a dedicated and multidisciplinary approach, like SLN biopsy and ILP. It is understandable that institutions treating few patients would not be organized to perform such procedures.

There were several important differences between centers regarding SLN biopsy. The tendency to use the Gamma Probe without Patent Blue dye in low-volume centers would not appear to be an important difference because the association of Patent Blue serves mainly to facilitate the surgical procedure. Regarding Breslow thicknesses >4 mm, interpretation of our data should consider the clinical studies on such patients. In fact, there is ongoing debate over the indication for SLN biopsy in such patients, some holding that the overall poor prognosis at this stage is no longer guided by lymph node involvement. This may be an excessively rigid interpretation lacking biological justification, since a negative SLN result would indicate better prognosis for a given Breslow thickness.

Regarding ILP, it is noteworthy that while more high-volume centers perform such procedures (24 vs. 11%), overall the number is very small. Where ILP is not performed, there is agreement in both types of centers that it be indicated for inoperable or rapidly relapsing metastases in transit. The significant difference between high-
and low-volume centers in requesting ILP for a first metastasis in transit (13 vs. 35%) is likely to be due to the level of experience with this pathology. Generally the indication for ILP is multiple or rapidly recurring metastases, which obviously is not the case for a first metastatic manifestation. When, instead, patients are not referred for ILP, both types of centers divide patients equally between medical and surgical treatments. ECT is being used with gradually increasing frequency and the methodology is established in the European Standard Operating Procedures of Electrochemotherapy (ESOPE) guidelines [23].

**Disclosure Statement**

The authors have no disclosure in relation to this subject.

**References**


