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Is 1 mm thickness sec. Breslow the correct cut-off for sentinel node biopsy in melanoma? Report of six cases of metastasis by thin melanoma.

AIM: To reassess selection criteria for Sentinel Lymph Node Biopsy (SLNB) in patients with thin melanoma (Breslow ≤ 1 mm).

MATERIAL OF STUDY: Between January 2004 and November 2010 we observed 6 patients with lymph node metastasis from early melanoma (Breslow ranging from 0.3 mm to 0.9 mm, not ulcerated tumor, mitosis/mm² < 1). Nobody had received a prior study of sentinel lymph node so all patients underwent enlarged lymphadenectomy of concerned lymphatic stations and cancer re-staging.

RESULTS: The pathological examination of lymph nodes has always confirmed metastatic melanoma. The average follow-up is currently 51,5 months: 3 of 6 patients presented recurrence that in one case led to death.

DISCUSSION: In the event of a thickness < 1 mm the probability of finding a positive sentinel lymph node is about 7%. Recent data have demonstrated a significant survival advantage to early therapeutic lymphadenectomy in melanoma.

CONCLUSIONS: Our experience, supported by the cases described and the literature, leads to propose the technique of SLNB to all patients with melanoma thicker than 0.5 mm, given the low morbidity and the important prognostic role of the procedure, in addition to the possibility of reducing the incidence of lymph node metastases.

KEY WORDS: Metastasis, Sentinel node, Thin melanoma

Background

The incidence of cutaneous melanoma continues to increase steadily¹, perhaps because of the intense screening programs, and approximately 70% of new cases of cutaneous melanoma are thin melanomas^{2,3}. Thin melanomas (T1a for AJCC, American Joint Committee

on Cancer), according to current guidelines, are considered highly curable with wide local excision alone⁴ and reported disease-free survival rates of 90%⁵. As tumor thickness is an important prognostic indicator in melanoma^{6,7}, thin tumors are generally considered to be at low risk of disease progression^{8,9}. Conversely some studies have found sentinel node metastases in a significant number of patients with thin lesions (Breslow thickness ≤ 1 mm)¹⁰⁻¹⁵. A recent study by Kalady et al., with more than 10.000 patients on a 30-year period, showed nodal or metastatic disease in approximately 15% of patients with thin melanoma¹⁶. On the basis of these assessments, even more surgeons advocate routine evaluation of the lymphatic basin in patients with thin melanomas.

Sentinel lymph node biopsy (SNB) is an accepted procedure to accurately stage a patient with a cutaneous melanoma, because it can determine the presence of

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(micro) metastases in the sentinel node. Indeed it has become the standard of care as a less invasive alternative to lymphadenectomy for evaluation of the nodal basin¹⁷. This has shown to be the most important predictor for survival in patients with a primary melanoma without clinical evidence for metastatic disease^{18,19}. Furthermore recent data have demonstrated a significant survival advantage to early therapeutic lymphadenectomy²⁰.

We report six cases of nodal metastasis by thin melanoma that were treated only with surgical excision, without the study of SLN, according to actual agreed guidelines. Moreover we expose how we deal with thin melanoma patients and which is our acknowledged cut-off point for performing an SNB, in the light of our experience and the literature to date.

Material and methods

Between January 2004 and November 2010 we observed 6 patients with lymph node metastasis from early melanoma (average Breslow of 0.78mm, ranging from 0.34 mm to 0.93 mm, not ulcerated tumor, mitosis/mm² < 1). All patients were biopsied with a margin of less than 1 cm and therefore re-operated to provide a greater margin of safety for cancer. No patient had received a prior study of sentinel lymph node.

1 melanoma of the abdominal region (male, 72 y.o., Breslow: 0.34 mm, Clark level IV, important regression areas) had inguinal lymph node metastasis. 1 melanoma of the back (female, 40 y.o., Breslow: 0.91 mm) interested in the ipsilateral groin. 1 melanoma of the upper limb (male, 56 y.o., Breslow: 0.93 mm) had ipsilateral axillary metastasis, lung and brain metastasis at PET/C.T.; died after 30 months of follow-up. 1 melanoma of the lower limb (male, 65 y.o., Breslow: 0.9 mm) had metastasis in ipsilateral groin and received Completion Lymph Node Dissection; after 18 months in-transit metastasis of the popliteal region, re-operated, still in follow-up with no signs of relapses. 1 melanoma of the lower limb (male, 48 y.o., Breslow: 0.77 mm) had metastatic ipsilateral groin; on the 15th month of follow-up developed a little lung metastasis that was operated; no relapses to date. 1 melanoma of the lower limb (female, 71 y.o., Breslow: 0.81 mm) had groin metastasis. The time of occurrence of lymph node metastases ranged between 6 and 20 months. We obtained the diagnostic confirmation by FNAC. All patients underwent enlarged lymphadenectomy of concerned lymphatic stations and cancer re-staging.

Results

The pathological examination of lymph nodes has always confirmed metastatic melanoma. All patients were sent

to the oncologist to undergo adjuvant therapy. The average follow-up of the sample, calculated up to January 2012, is currently 51,5 months (range: 14-96 months). The patient who died had a widespread metastatic disease unresponsive to chemotherapy. All the other patients are still in follow-up and without signs of relapses.

Discussion

Current guidelines for the treatment of melanoma include the implementation of the sentinel node biopsy only in cases of primary tumor thickness ≥ 1 mm sec. Breslow or in case of ulcerated tumor, or even in the case of Breslow < 1 mm with evidence of one or more mitoses/mm². Before it was thought that thin melanoma rarely recur after simple excision, specifically melanomas ≤ 75 mm⁴. There has been an increasing number of reported recurrences and fatal outcomes for patients with melanomas ≤ 75 mm¹⁶. In 2002, the American Joint Committee on Cancer (AJCC) revised the melanoma staging system, revising the definition of thin melanomas from lesions ≤ 75 mm to those ≤ 1.0 mm. Both Clark level IV and V and ulceration were included in the staging as prognostic factors for thin lesions (T1), as both appeared to be associated with a significant reduction in survival. In 2009, the AJCC replaced Clark level with mitotic rate as a prognostic factor.

Currently SLNB is widely accepted as a highly accurate method for nodal staging of patients with melanoma²¹. Is now accepted that in the event of a thickness < 1 mm the probability of finding a positive sentinel lymph node is about 7%²², but the application of SLNB to patients with thin melanoma remains highly debated, primarily due to the validity, cost-effectiveness, and indications²¹. Some studies have reported that SLN positivity in patients with thin melanomas is an independent predictor of poorer survival^{13,26} but other studies (including a meta-analysis) have found no correlation between SLN status and survival in these patients^{29,30}.

At present, most of the authors believe that the evaluation of the lymphatic basin in cutaneous melanoma is imperative to overall long-term prognosis²³. The studies of clinicopathologic factors associated with occult nodal metastasis in patients with thin primary cutaneous melanomas have yielded conflicting results. The factors identified beyond the AJCC revised melanoma staging system (Breslow thickness, ulceration, Clark level and mitotic index) include age, gender, primary site, lymphatic response, vertical growth phase, angiolymphatic spread and regression^{10,12,13,15,24-28}. In a recent study of Murali et al.²² SLNB was negative in all patients with melanomas 0.50 mm or less in Breslow thickness and the SLN positivity rates in tumors measuring 0.51 to 0.75 mm, 0.76 to 0.90 mm, and 0.91 to 1.00 mm were 3.8%, 5.3%, and 10.3%, respectively.

Conclusions

Our experience, supported by the cases described and the literature, leads to propose the technique of SLNB to all patients with a tumor thicker than 0.5 mm sec. Breslow, given the low morbidity, the important prognostic role and the likely therapeutic role of the procedure, with the possibility of realizing an earlier therapeutic lymphadenectomy²⁰.

Patients with thin tumors should be informed of their likelihood of SLN positivity. They may then decide whether or not they wish to have a SLNB: almost all of our patients decide to receive the procedure. For tumors thinner than 0.5 mm we evaluate case-by-case, especially considering the clinicopathologic factors mentioned earlier. Although there is no agreement about these we inform the patient on the risks and possible benefits and decide together. Certainly more studies are needed to establish selection criteria for SLNB in thin melanoma lesions.

Riassunto

INTRODUZIONE: Secondo le attuali linee guida, il trattamento di scelta per un paziente con melanoma sottile (T1a) è limitato alla semplice escissione chirurgica con margine superiore al centimetro. Ultimamente però un numero crescente di chirurghi è orientato a trattare queste lesioni iniziali come quelle più spesse, includendo la biopsia del linfonodo sentinella. Noi stessi abbiamo verificato in più casi la possibilità di metastasi da melanoma con spessore inferiore al millimetro.

MATERIALI E METODI: Nel periodo compreso tra Gennaio 2004 e Novembre 2010 abbiamo osservato 6 pazienti con metastasi linfonodali da melanoma sottile (Breslow variabile da 0.3mm a 0.9mm, tumore non ulcerato, mitosi/mmq<1). Tutti i pazienti erano stati sottoposti a biopsia escissionale semplice e successivamente rioperati per garantire un margine superiore al centimetro. Nessuno aveva effettuato la biopsia del linfonodo sentinella.

Il tempo di insorgenza delle metastasi variava tra 6 e 20 mesi. Abbiamo sottoposto tutti i pazienti a FNAC per la conferma diagnostica. Tutti i pazienti sono stati trattati con linfoadenectomia delle stazioni linfatiche interessate e ristadiazione oncologica.

RISULTATI: L'esame istologico dei linfonodi ha sempre confermato melanoma metastatico. Tutti i pazienti sono stati inviati all'oncologo per la terapia adiuvante. Il follow-up medio del campione, calcolato fino a Gennaio 2012, è 51,5 mesi. In tre pazienti è stata rilevata malattia metastatica in sedi differenti da quelle da noi operate, che in un caso ha condotto all'exitus. Nei restanti tre casi, ancora in follow-up, non c'è evidenza di malattia.

DISCUSSIONE: Le attuali linee guida per il trattamento del melanoma prevedono l'esecuzione della biopsia del linfonodo sentinella in caso di tumore primitivo con spesso-

re ≥ 1 mm sec. Breslow o in caso di tumore ulcerato o in caso di Breslow < 1 mm con una o più mitosi/mmq. Esistono in letteratura diversi lavori che indicano come la percentuale di metastasi linfonodali e/o a distanza in pazienti con melanoma sottile raggiunge valori anche del 15%; la positività del linfonodo sentinella è riportata intorno al 7%. Recenti studi multicentrici mettono in luce il miglioramento della sopravvivenza dei pazienti trattati precocemente con linfoadenectomia.

CONCLUSIONI: Alla luce di queste considerazioni si rendono necessari nuovi criteri di selezione per l'esecuzione della biopsia del linfonodo sentinella nei pazienti affetti da melanoma sottile, considerata la bassa morbilità della procedura a fronte di un importante ruolo prognostico e del vantaggio terapeutico della linfoadenectomia precoce.

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