Chapter 15

After Surgery: Follow-Up Guidelines of Melanoma Patients

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http://dx.doi.org/10.5772/55335

1. Introduction

There are several main reasons to begin a follow-up schedule after surgical treatment of the primary cutaneous lesion in patients affected by melanoma.

The main goal is the early detection of disease recurrence, even if the impact of a prompt treatment on prognosis is still debated (Barth et al 1995, Atkins et al 2008, Garbe et al 2008). Several authors believe that early detection of asymptomatic metastases does not affect overall survival (Barth et al 1995, Atkins et al 2008). Others (Garbe et al 2008) showed a clear survival benefit for an early with respect to late metastases detection, with a 3-year survival rate of 76%, compared to the 38% of patients with late diagnosis. The early relapse recognition might lead to a more complete and less invasive surgical treatment, with potential benefits for the patient.

A loco-regional or distant spreading is a not uncommon event that arises in a percentage of patients varying from 15 to 35%. Indeed, in melanoma patients the risk of spreading is strictly related to the disease stage at diagnosis, and an effective follow-up program should taken in account both the AJCC classification (Balch et al 2009; Piris, Mihm & Duncan 2011) (Table 1) and the different patterns of metastatic dissemination related to site of primary, gender and age of patients (Quaglino et al 2007). On the basis of recently updated AJCC classification (Balch et al 2009), for patients affected by localized stage I or II melanomas, tumour thickness, mitotic rate and ulceration are considered the most relevant prognostic parameters; ulceration and thickness of primary tumour maintain a role as predictive independent factors on survival also in stage III patients, together to the number of involved lymph nodes, whereas for patients with distant metastases, elevated values of serum lactate dehydrogenase (LDH) define a category with poor prognosis. According to the primary location, no difference in the relapse

rate was found for melanomas located on the head-neck, back, anterior trunk, upper limb and thigh-leg; conversely, a primary melanoma located to the foot was associated to a statistically significant higher relapse rate with respect to all the other sites (Quaglino et al 2007). As regard the first site of metastatic spreading, patients with a lower limb primary melanoma showed more frequently loco-regional metastases, whereas distant spreading was mainly observed in patients with melanoma located in the trunk (Savoia et al 2009). More in details, lower limb location showed a low incidence of visceral metastases as first site of relapse, irrespectively of the AJCC stage, compared to all other body sites (Quaglino et al 2007).

Clinical Staging				Pathological Staging			
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	any T	N 1-3	M0	IIIA	T1-T4a	N1a/2a	M0
				IIIB	T1-T4b	N1a/2a	M0
					T1-T4a	N1b/2b	M0
					T1-T4a/b	N2c	M0
				IIIC	T1-T4b	N1b/2b/2c	M0
					any T	N3	M0
IV	any T	any N	M 1	IV	any T	any N	M 1

Table 1. Clinical and pathological staging, AJCC 2009.

The majority of guidelines encourage frequent clinical and radiological examination during the first 5 years from the diagnosis, due to the fact that almost 90% of all metastases occur during this period (Dummer et al 2011). However, it has been demonstrated that the time course of first relapse depend to the AJCC stage: the progressive decrease of relapse trend and the subsequent plateau is reached earlier in stage IA (after the second year) and later in stage IIB/IIC (from 5th to 8th year); moreover, distant relapses as first site of recurrences showed a low (<1.5%), but constant annual incidence, even beyond 10 years from diagnosis (Quaglino et al 2007); these data support the opinion of several authors who believe that a lifelong surveillance should be recommended (Garbe et al 2008, Dummer et al 2011).

http://dx.doi.org/10.5772/55335

The second reason to include melanoma patients in a follow-up program is the early identification of possible further primary melanomas or other skin tumours. Development of more than one primary melanoma in a sole patient is in fact a relatively common and well-recognized phenomenon; its frequency varies from 1.2 to 8.2% in the most recent published series (Savoia et al 2012) and it is probably due to a specific genetic background. In the majority of cases recently described (Bower et al 2010; Doubrowsky & Menzies 2003), there is a significant reduction in mean Breslow's thickness from the first to the second and successive primary melanomas, with a consequent favourable impact on prognosis. This is mainly resulting from well-timed diagnosis during follow-up programs.

Some melanoma patients also have an increased risk to develop non-melanoma skin tumours. In particular, 35% of patients affected by lentigo maligna melanomas develops others cutaneous malignancies within 5 years from the first diagnosis (Farshad et al 2002); this is probably related to the fact that this melanoma type prefers elderly patients with a chronic actinic skin damage. Also the relatively good prognosis of these patients may play a role.

Finally, a follow-up schedule should also perform an educational role, with the purpose of having a favourable impact on the population health and quality of life (Dummer et al 2010). Melanoma patients should be instructed not only in regular self-examination of the skin but also to avoid sunburns and prolonged unprotected solar or artificial ultraviolet exposure. Patients must also be aware that family members have an increased melanoma risk, consequent to both skin phototype and genetic background.

To date, even if these basic principles are approved, there is not a complete international agreement about the better follow-up schedule, with several differences in timing and duration between different Countries.

1.1. Imaging studies

Imaging studies can play a central role in the early detection of melanoma progression, allowing to a better treatment for patients. However, it is not generally accepted that the an early recognition of asymptomatic metastatic disease can affect the overall survival (Atkins et al 2008, Bichakjian et al 2011) and many imaging studies are considered uneconomical and not entirely risk-less for the patient. Thus, many international guidelines accept an imaging surveillance only in patients considered at higher risk of recurrence, as well stage IIIB and above, not approving the execution of instrumental tests in asymptomatic low risk patients (Marsden et al 2010, Bichakjian et al 2011). However, while ultrasonography is not harmful, relatively cheap and easy to perform, and can routinely be used not only in advanced, but also in stage I-II patients. In particular, even if sonography is operator-dependent, it remains more sensitive than clinical examination alone in the early identification of nodal metastases; sensitivity of ultrasound can be further improved by fine needle aspiration cytology, reaching the 80% in some selected series (Voit et al 2006, Negrier et al 2005). Higher sensitivity can be achieved only by sentinel node mapping. On the contrary, ultrasonography is relatively ineffective in detecting distant metastases: the calculated sensitivity for abdominal ultrasonography was only 53%, in comparison with 85% for CT scan (Forschner et al 2010). Similarly, traditional chest X-ray is less sensitive than CT-scan in the detection of lung metastases (Negrier et al 2005).

As a consequence of the high metabolic rate of melanoma cells, PET-CT can be useful to detect metastases in stage IIC or stage III patients, as well as in disease monitoring in stage IV patients (Bastiaannet et al 2009). This technique has a high sensitivity and allows an accurate study of the whole body, except the brain. The value of PET-CT in the follow-up of melanoma patients is supported by the recommendations from the update Swiss guidelines (Dummer et al 2011), that encourage the use of PET-CTC every 6-12 months for the first 5 years from diagnosis in stage IIC or stage III patients and by the fact that Swiss health insurances cover this imaging technique. However, PET-CT is not effective in the detection of positive sentinel lymph nodes in patients with primary melanomas (Negrier et al 2005, Clark et al 2006, Maubec et al 2007, Marsden et al 2011).

1.2. Screening blood tests

Routinely laboratory investigations have a relatively limited role in melanoma follow-up programs and are usually not recommended in asymptomatic patients affected by localized cutaneous melanoma of any thickness (Marsed et al 2010, Negrier et al 2005, Bichakjian et al 2011). However, recent advances in molecular biology techniques have permitted, in last years, the identification of several molecules with a potential prognostic and diagnostic role.

Melanoma patients with advanced disease share elevated lactate dehydrogenase (LDH) serum levels. Nevertheless, this marker act as an unfavourable prognostic factor only in stage IV disease and high LDH levels are also demonstrated in unspecific tissue necrosis conditions, such as haemolysis or myocardial infarction. So, the role of LDH in detection and monitoring of metastatic disease is still controversial (Wang et al 2004). As we mentioned in the previous paragraphs, in the updated AJCC classification (Balch et al 2009), for patients with distant metastases the presence of elevated lactate dehydrogenase serum levels define the M category, characterized by a poor prognosis.

Tyrosinase is the key enzyme responsible for the first two steps of melanin biosynthesis and is considered one of the most specific markers in melanocytic differentiation, as its expression is limited only to cells of neural crest derivation, such as melanocytes, melanoma cells and Schwann cells. Tyrosinase detection by reverse transcription-polymerase chain reaction (RT-PCR) analysis was initially applied to the detection of melanoma cells in SLN (Li et al 2000). More recently, the detection of tyrosinase transcripts using the nested RT-PCR has been proposed to identify the presence of melanoma cells in the peripheral blood in patients who have undergone radical surgery (Osella et al 2000), as well as a potential additional tool for the identification of melanoma cells in bone marrow and biological fluids other than blood (Gossein et al 1996, Hoon et al 1997, Osella et al 2003). However, the real diagnostic and prognostic relevance of this test is still controversial and its role in clinical practice is not yet fully defined.

The S-100 calcium binding protein represent an high-sensitive marker for melanocytic lesions, even if is no specific, since it stain either melanocytes or Langerhans and Schwann cells. In several studies it has been demonstrated to correlate with the tumour invasiveness in melanoma patients. Even if literature data about the melanoma–associated antigen S-100 are still controversial, the majority of published studies report that the percentage of patients with high S-100 levels increase progressively from stage I-II (0-12%) up to stage IV (Schultz et al 1998, Kaskel et al 1999, Jury et al 2000). The sensitivity and specificity of this marker in the identifi-

http://dx.doi.org/10.5772/55335

cation of patients with a metastatic spread seems to be higher when compared with tyrosinase; the 64% of patients with serum S-100 levels exceeding 0.2mg/L showed distant metastases, confirmed by FDG-PET/CT scan (Forschner et al 2010). S-100 could play a role also in diagnosis of lymph node involvement: nodal metastases were identified in 19% of patients with high serum S-100 levels (Forschner et al 2010). Actually, S-100 is considered a good marker for melanoma relapse, especially for disease free stage III patients (Beyler et al 2006; Kruijff et al 2010), whereas in advanced stage patients, S-100 levels are related with treatment response and disease relapse (Garbe & Leiter 2003). The updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma (Dummer et al 2011) suggest to monitorate S-100 levels every 6-12 months for the first 5 years from melanoma diagnosis in all stage II and III patients; for stage IV patients, timing of sampling for S-100 detection should be individualized for single patients.

Elevated serum levels of cytokines (IL-6, -8 and -10), soluble IL-2 receptor and soluble adhesion molecule (sICAM and sVCAM) (Eton et al 1998) has also been proposed as progression markers in melanoma patients; however, the relatively low sensibility and specificity of these molecules, together with their low cost-effectiveness ratio make them little used in clinical practice.

To date, others melanoma-associated antigens, such as melanoma inhibitory activity (MIA) and neuron-specific enolase (NSE) or molecular markers, including MART-1/Melan-A, gp100, TRP-1 and -2 showed a lower sensitivity and specificity and literature data regarding their potential role in the early detection of metastatic disease are still controversial. A multimarkers analysis appears to be associated with a sensitivity increase in the detection of circulating melanoma cells, but the impact of these data on patient's survival has not yet been conclusively defined.

2. Follow-up schedules according melanoma stage

2.1. In situ melanoma

Patients with a surgically treated in situ melanoma have no risk of metastases; so, the follow-up program should not include radiological examinations. It is also debated if clinical follow-up visits are needed. The 2010 UK guidelines of the British Association of Dermatologists recommend only a return visit after the complete excision to explain diagnosis and the education of patients to the self-examination for a new primary melanoma (Marseden et al 2010). Others authors recommend a closer follow up with a clinical check of the whole skin every 6-12 months (Dummer et al 2011). Even if the majority of multiple primary melanomas were identified within 1 year from the first diagnosis, a relevant percentage developed after 5 or also 10 year from the primary excision (Savoia et al 2012; van der Leest et al 2012), especially in younger patients. Consequently, in our opinion in consideration of the favourable prognosis of patients with a previous in situ melanoma, follow-up visits should be continuated, with the purpose of early diagnosis of possible further primary melanomas. Patients should also be instructed in avoidance of sunburn and informed that their consanguineous have an increased melanoma risk.

2.2. Stage IA melanoma

The 5-year overall survival of stage IA patients is over 90%, with virtually no risk of recurrences for patients with melanomas < 0.5 mm and a slightly worse prognosis for those with non-ulcerated 0.5-1 mm thick primary tumour (Einwachter-Thompson & MacKie 2008).

Considering this relatively low risk of disease progression, the revised UK guidelines for the management of melanoma (Marsden et al 2010) not recommended routinely imaging staging, due to the low true-positive rate and the high false-positive rate. According to the UK guidelines, patients should underwent to a series of two to four visits over the first years from the primary excision, in order to teach self-examination and then discharged from a regular follow-up. Similarly, the National French federation of cancer centres and the French society of dermatology suggest only periodical clinical examinations for patients in this clinical stage (Negrier et al 2005). Clinical follow-up at 6 monthly intervals, with the possible additional use of of ultrasonography, is considered appropriate by the majority of others groups (Quaglino et al 2007; Garbe et al 2010). Moreover, abdominal ultrasound imaging and chest x-ray are performed by many physicians to have baseline images for the further follow-up (Forschner et al 2010).

Routinely serological tests are not generally recommended in melanomas in the initial stage; however, the Catalan guidelines (Mangas et al 2010) suggest to perform at diagnosis complete blood count and biochemistry (including alkaline phosphatase, gamma-glutamyltransferase and lactate dehydrogenase) together with detection of molecular markers such as S-100, MIA and tyrosinase in all patients excepted those affected by melanoma in situ. Standard blood workup and LDH measurement should be repeated 6-monthly for the first 2 years and annualy for the following 2 years (Mangas et al 2010).

2.3. Stage IB and IIA melanoma

In this group of patients the risk of recurrence is of 15-35%, mainly within the first 5 years from diagnosis. A follow-up examination every 3 months at least for the first 5-years is recommended from the European consensus-based interdisciplinary guidelines (Garbe et al 2010), in order to detect early any loco-regional recurrences; a similar schedule is proposed also by Italian groups (Quaglino et al 2007). UK guidelines (Marsden et al 2010) admit checks every 3 months only for the first 3 years; then, patients should be instructed to self-examination also for loco regional metastases and visited only once every 6 months to 5 years. No routine instrumental investigations are required for this group of patients according UK follow-up schedule. Several studies demonstrated that ultrasonography of in-transit routes and regional lymph nodes are more sensitive than physical examination (89.2% vs. 71.4%) in the detection of nodal metastases in patients with an intermediate melanoma thickness (Blum et al 2000, Garbe et al 2003, Quaglino et al 2007). So, patients with a tumour thickness of 1 mm or more should be asked to undergo lymph node ultrasound imaging every 6 months (Forschner et al 2010). Ultrasonography of regional lymph node every 3-6 months within the first 5 years from diagnosis is suggested only for stage II patients also by French guidelines (Negrier et al 2005), whereas others imaging procedures are considered as optional. The clinical experience of major Italian referral centres for melanoma suggests performing a CT scan annually for the first 5 years also in stage IIA.

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Screening blood tests are suggested only by Catalan guidelines, that propose standard blood workup and LDH detection 2 times a year for the first 5 years and then annually for the following 2 (Mangas et al 2010).

2.4. Stage IIB and IIC melanoma

UK guideline (Marsden et al 2010) did not recommend routine investigations also for stage IIB and IIC patients, despite the higher risk of recurrences (40-70%, above all in years 2-4); only self-examination and clinical visits 3-monthly for 3 years and 6-monthly to 5 years are suggested.

For stage IIC patients, as well for the more advanced stages, both Italian (Quaglino et al 2007) and French guidelines recommended not only a regional ultrasonography two times a year, but also brain, chest and abdomen CT scan that should be carried out annually for the first 5 years (Negrier et al 2005). Also for this group of patients, screening blood tests almost 2 times a years are recommended by Catalan authors (Mangas et al 2010).

Table 2 and 3 compare different follow-up visit schedules from European and US guidelines.

	Clinical examination schedule (years 1-5 from diagnosis)					
Stage*	Dummer, 2011	Marsden, 2010	Mangas, 2010	Garbe, 2009	Quaglino, 2008	Négrier, 2005
In situ	f-u visit every 6-12 months	*no f-u visit required*	*f-u visit every 12 months*	*no f-u visit required*	*f-u visit every 12 months*	*NA*
IA	visit every 6 months	*visit every 3-4 months, then discharged*	visit every 3/6 months†	visit every 6 months	visit every 6 months	visit every 6 months
IB	visit every 3 months	visit every 3 months**	visit every 3/6 months†	visit every 3/6 months[1]	visit every 6 months	visit every 6 months
IIA	visit every 3 months	Visit every 3 months**	visit every 3/6 months†	visit every 3 months	visit every 4 months	visit every 3 months
IIB	visit every 3 months	visit every 3 months**	visit every 3 months†	visit every 3 months	visit every 4 months	visit every 3 months
IIC	visit every 3 months	visit every 3 months**	visit every 3 months†	visit every 3 months	visit every 4 months	visit every 3 months

* revised AJCC Classification.

** visit every 3 months for the first 3 years, then 6-monthly to 5 year.

[1]In consideration of Breslow thickness: for melanoma <1mm every 6 months; for melanoma >1 mm every 3 months.

† visit every 3 months for the first 2 years, then 6-monthly to 5 year.

Table 2. Clinical examination schedule (years 1-5 from diagnosis)

	Imaging examination schedule (years 1-5 from diagnosis)					
Stage*	Dummer, 2011	Marsden, 2010	Mangas, 2010	Garbe, 2009	Quaglino, 2008	Négrier, 2005
In situ	*Not required*	*Not required*	*Not required*	*Not required*	*Not required*	*NA*
IA	*Regional sonography every 6-12 months*	*No routine investigation required*	*Chest X-ray every 12 months; abdominal sonography every 12 months (optional)*	*No routine investigation required***	*Regional sonography every 12 months*	*No routine investigation required*
IB	*Regional sonography every 6-12 months*	*No routine investigation required*	*Chest X-ray every 6 months; abdominal sonography every 6 months (optional)*†	*No routine investigation required***	*Regional and abdomen sonography every 12 months; chest X-ray every 12 months*	*No routine investigation required*
IIA	*Regional sonography every 6-12 months. Abdominal sonography and chest X-ray individually*	*No routine investigation required*	*Chest X-ray every 6 months; abdominal sonography every 6 months (optional)*†	*No routine investigation required***	*Regional and abdomen sonography every 12 months; chest X-ray every 12 months; TC scan every 24 months*	Regional sonography every 3-6 months.
IIB	*Regional sonography every 6-12 months. Abdominal sonography and chest X-ray individually. CT scan every 6-12 mo*	*No routine investigation required*	*CT scan every 6/12 months*†	*No routine investigation required***	*Regional and abdomen sonography every 12 months; chest X-ray every 12 months; CT scan every 12 months*	Regional sonography every 3-6 months.
IIC	*Regional sonography every 6 months. Abdominal sonography and chest X-ray individually. CT scan every 6-12 mo*	*No routine investigation required*	*CT scan every 6/12 months*†	*No routine investigation required*	*Regional and abdomen sonography every 12 months; chest X-ray every 12 months*	Regional sonography every 3-6 months. PET-CT, and CT scan individually

* revised AJCC Classification.

** sonography individually

† every 6 months for the first 3 years, then annually to 5 year

Table 3. Imaging examination schedule (years 1-5 from diagnosis)

2.5. Stage III melanoma

At the initial visit prior to surgical treatment, brain, chest, abdominal and pelvic CT is recommended, in order to exclude visceral involvement; PET-CT and cranial MRI may be

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proposed as alternative; Catalan guidelines suggest also a bone scintigraphy as optional (Mangas et al 2010).

Due to the high risk of visceral spreading in stage III patients, close follow-up and imaging investigations are accepted by almost all guidelines (Garbe et al 2010, Marseden et al 2010, Dummer et al 2010, Forschner et al 2010, Romano et al 2010). Head, chest and abdomen CT scan is normally useful to detect metastases, with higher sensitivity than ultrasound imaging; PET-CT can also be used alternatively (Negrier et al 2005). However, some other authors consider imaging investigation as optional in absence of specific sign or symptoms (Coit et al 2009).

Literature data reports also a wide range of follow-up approaches, without precise rules for timing and duration. A close follow-up regimen was proposed by Garbe et al (2003), with clinical visits every 3 months for the first 5 year and then every 6 months up to 10 years after lymph node dissection and instrumental examination (CT scan, PET-CT, chest x-ray or abdominal and lymph nodal ultrasound) every 6 months. In the sample of patients examined, a disease progression was detected by physical examination in almost the half of cases, and by imaging in more than one third of cases; on the contrary, relapses were rarely early discovered in patients outside of the scheduled follow-up. In this work, Garbe report a better 5-year survival in patients with early diagnosis of recurrences compared to that of patients with unresectable metastases, supporting the validity of a close follow-up program (Garbe et al 2003). Other similar follow-up programs (Hoffman et al 2002, Poo-Hwu 1999), with a relatively high frequency of visits (3-monthly for almost 3 years), come to similar results. The UK guidelines (Marsden et al 2010) suggest a 6-monthly follow-up to 5 years and then annually to 10 years, whereas regular follow-up every 6 months with whole body imaging is recommended by others (Forschner et al 2010).

The study recently published by Romano et al. (2010), focused on stage III patients, evaluate also the substage. For stage IIIA patients, the risk of loco-regional relapse was less than 5% after 3 years from stage IIIA diagnosis, suggesting that beyond this point of time clinical examinations may be referred. Similarly, the risk of loco-regional relapse dropped to less then 5% after 2 years from diagnosis for stage IIIB patients and after 7 months in stage IIIC. Stage IIIC patients are the subset with higher risk of visceral spreading, with a 36% of patients that develop the first relapse in the brain; so, this subgroup of patients should be subjected to imaging examination more fequently

Even if routinely blood tests usually fail in the early detection of metastases, in stage III melanoma patients tyrosinase (Osella- Abate et al 2003) or S100 (Dummer et al 2010, Forschner et al 2010) has been demonstrated good marker for relapse.

2.6. Stage IV melanoma

No international follow-up guidelines are available for patients with metastatic disease. The management strategy should be patient-taylored on the basis of primary melanoma characteristics, metastases site, age and general conditions.

The development in the last few years of a novel class of targeted drugs (such as ipilimumab, vemurafenib, imatinib) with an impact on survival, had an important effect on the management of these patients. C-kit and BRAF mutational state have to be evaluated in order to select patients who can underwent this targeted therapies; also the identification of subgroups of patients with different clinical behaviours is important for the right therapeutical choice, especially for the drugs that need time to act (e.g anti-CTLA-4).

3. Conclusions

The main follow-up goal is the early detection of disease recurrence, which can allow a prompt treatment with a potential prognostic benefit.

To date an international agreement about the most suitable follow-up guidelines for patients who underwent a surgical excision of a primary melanoma is still lacking. Several national guidelines are available, but the schedules differ as to the time frequency of both clinical visits and imaging. However it is generally accepted that the frequency of clinical examinations must to be decided on the basis of the AJCC stage at diagnosis and that a closer follow-up should required in the first five years from diagnosis due to the higher risk of recurrence observed in this time range. Regional node ultrasound is an useful tool for the detection of suspected superficial adenopathies.

On the other hand, the role of imaging for the detection of visceral metastases in asymptomatic patients is still a challenge: for low risk (IA) melanomas no routine investigations could be required; sonography is generally used in follow up of intermediate/high risk melanoma patients (IB to IIA), whereas the use of CT and PET scan is limited to patients with an higher relapse risk (stage IIC or higher). It is generally accepted that the follow up's strategy for disease-free stage III/IV patients, must to be tailored on the basis of clinical characteristics and general conditions.

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References

[1] Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA, Sondak VK &. Kirkwood JM. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine,

and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2008; 26:5748-54.

[2] Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Kirkwood JM, McMasters KM, Mihm MC Jr, Morton DL, Ross MI, Sober AJ & Sondak VK. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27: 6199-6206.

[3] Barth A, Wanek LA & Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. J Am Coll Surg 1995; 181:193-201.

[4] Bastiaannet E, Wobbes T, Hoekstra OS, van der Jagt EJ, Brouwers AH, Koelemij R, de Klerk JM, Oyen WJ, Meijer S, & Hoekstra HJ. Prospective comparison of [18f]fluorodeoxyglucose positron emission tomography and computed tomography in patients with melanoma with palpable lymph node metastases: Diagnostic accuracy and impact on treatment. J Clin Oncol. 2009; 27:4774–80.

[5] Beyeler M, Waldispuhl S, Strobel K, Joller-Jemelka HI, Burg G & Dummer R. Detection of melanoma relapse: First comparative analysis on imaging techniques versus s100 protein. Dermatology. 2006; 213:187–91.

[6] Bichakjian C K, Halpern AC , Johnson TM, Foote Hood A , Grichnik JM., Swetter SM., Tsao H , Holloway Barbosa V, Chuang TY, Duvic M, Ho VC, Sober AJ, Beutner KR, Bhushan R & Smith Begolka K. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2011; 1032-1047.

[7] Blum A, Schlagenhauff B, StroebelW, Breuninger H, Rassner G & Garbe C. Ultrasound examination of regional lymph nodes significantly improves early detection of locoregional metastases during the follow-up of patients with cutaneous melanoma: results of a prospective study of 1288 patients. Cancer 2000; 88:2534-9.

[8] Bower MR, Scoggins CR, Martin RC 2nd, Mays MP, Edwards MJ, Reintgen DS, Ross MI, Urist MM, Noyes RD, Sussman JJ, Hagendoorn LJ, Stromberg AJ & McMasters K .Second primary melanomas: incidence and outcome. Am Surg. 2010; 76(7):675-81.

[9] Clark PB, Soo V, Kraas J, Shen P & Levine EA. Futility of fluorodeoxyglucose F 18 positron emission tomography in initial evaluation of patients with T2 to T4 melanoma. Arch Surg 2006;141:284e8.

[10] Coit DG, Andtbacka R, Anker CJ, Bichakjian CK, Carson WE 3rd, Daud A, Dilawari RA, Dimaio D, Guild V, Halpern AC, Hodi FS Jr, Kelley MC, Khushalani NI, Kudchadkar RR, Lange JR, Lind A, Martini MC, Olszanski AJ, Pruitt SK, Ross MI, Swetter SM, Tanabe KK, Thompson JA, Trisal V & Urist MM; National Comprehensive Cancer Network : Melanoma. J Natl Compr Canc Netw 2009 7:250-275.

[11] Doubrovsky A & Menzies SW. Enhanced survival in patients with multiple primary melanoma.Arch Dermatol. 2003;139(8):1013-8.

[12] Dummer R, Guggenheim M, Arnold WA, Braun R & von Moos R. Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. Eu J Med Sci 2011; 141:w13320.

[13] Einwachter-Thompson J & MacKie RM. An evidence base for reconsidering current follow-up guidelines for patients with cutaneous melanoma less than 0.5 mm thick at diagnosis. Br J Dermatol 2008;159:337e41.

[14] Eton O, Legha SS, Moon TE, Buzaid AC, Papadopoulos NE, Plager C, Burgess AM, Bedikian AY, Ring S, Dong Q, Glassman AB, Balch CM & Benjamin RS. Prognostic factors for survival of patients treated systemically for disseminated melanoma. J. Clin. Oncol. 1998; 16(3), 1103–1111.

[15] Farshad A, Burg G, Panizzon R & Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using grenz or soft x-rays. Br J Dermatol.2002; 146:1042–1046.

[16] Forschner A, Eigentler TK, Pflugfelder A, Leiter U, Weide B, Held L, Meier F & Garbe C. Melanoma staging: facts and controversies. Clin Dermatol. 2010;28(3): 275-80.

[17] Garbe C, Leiter U, Ellwanger U, Blaheta HJ, Meier F & Schittek B. Diagnostic value and prognostic significance of protein S-100β, melanomainhibitory activity, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction in the follow-up of high-risk melanoma patients. Cancer 2003; 97(7), 1737–1745.

[18] Garbe C, & Leiter U. In reply: Prospective evaluation of a follow-up schedule in 2,008 patients with cutaneous melanoma: recommendations for an effective follow-up strategy. J Clin Oncol 2003; 21:3706-7.

[19] Garbe C, Schadendorf D, Stolz W, Volkenandt M, Reinhold U, Kortmann RD, Kettelhack C, Frerich B, Keilholz U, Dummer R, Sebastian G, Tilgen W, Schuler G, Mackensen A, Kaufmann R & Hauschild A. Short german guidelines: Malignant melanoma. J Dtsch Dermatol Ges. 2008; 6(Suppl 1):S9–S14.

[20] Ghossein RA, Coit D, Brennan M, Zhang ZF, Wang Y, Bhattacharya S, Houghton A & Rosai J. Prognostic significance of peripheral blood and bone marrow tyrosinase messenger RNA in malignant melanoma. Clin Canc Res 1998; 4, 419-428.

[21] Hofmann U, Szedlak M, Rittgen W, Jung EG, Schadendorf D : Primary staging and follow-up in melanoma patients: Monocenter evaluation of methods, costs and patient survival. Br J Cancer 2002; 87:151-157.

[22] Hoon DS, Wang Y, Dale PS, Conrad AJ, Schmid P, Garrison D, Kuo C, Foshag LJ, Nizze AJ & Morton DL. Detection of occult melanoma cells in blood with a multiple-marker polymerase chain reaction assay. J Clin. Oncol 1995; 13, 2109-2116.

[23] Kaskel P, Berking C, Sander S, Volkenandt M, Peter RU & Krahn G. S-100 protein in peripheral blood: a marker for melanoma metastases: a prospective 2- center study of 570 patients with melanoma. J Am Acad Dermatol. 1999; 41(6), 962–969.

[24] Kruijff S, Bastiaannet E, Muller Kobold AC, van Ginkel RJ, Suurmeijer AJ & Hoekstra HJ. Erratum to: S-100b concentrations predict disease free survival in stage iii melanoma patients. Ann Surg Oncol. 2010; 16(12):3455-62.

[25] Jury CS, McAllister EJ & MacKie RM. Rising levels of serum S100 protein precede other evidence of disease progression in patients with malignant melanoma. Br. J. Dermatol. 2000; 143(2), 269–274.

[26] Li W, Stall A, Shivers SC, Lin J, Haddad F, Messina J, Glass LF, Lyman G, Reintgen DS: Clinical relevance of molecular staging for melanoma: comparison of RT-PCR and immunohistochemistry staining in sentinel lymph nodes of patients with melanoma. Ann. Surg. 2000; 231, 795–803.

[27] Mangas C, Paradelo C, Puig S, Gallardo F, Marcoval J, Azon A, Bartralot R, Bel S, Bigatà X, Curcó N, Dalmau J, del Pozo LJ, Ferrándiz C, Formigón M, González A, Just M, Llambrich A, Llistosella E, Malvehy J, Martí RM, Nogués ME, Pedragosa R, Rocamora V, Sàbat M & Salleras M. Initial evaluation, diagnosis, staging, treatment, and follow-up of patients with primary cutaneous malignant melanoma. Consensus statement of the Network of Catalan and Balearic Melanoma Centers Actas Dermosifiliogr. 2010;101(2):129-42.

[28] Maubec E, Lumbroso J, Masson F, Suciu V, Kolb F, Mamelle G, Cavalcanti A, Boitier F, Spatz A, Aupérin A, Leboulleux S & Avril MF. F-18 fluorodeoxy-Dglucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm. Melanoma Res 2007;17:147e54.

[29] Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH, Gore ME, Lorigan P, Mackie R, Nathan P, Peach H, Powell B & Walker C. Revised UK guidelines for the management of cutaneous melanoma 2010. J Plast Reconstr Aesthet Surg. 2010;63(9):1401-19.

[30] Négrier S, Saiag P, Guillot B, Verola O, Avril MF, Bailly C, Cupissol D, Dalac S, Danino A, Dreno B, Grob JJ, Leccia MT, Renaud-Vilmer C &Bosquet L. Guidelines for clinical practice: Standards, Options and Recommendations 2005 for the management of adult patients exhibiting an M0 cutaneous melanoma, full report. National Federation of Cancer Campaign Centers. French Dermatology Society. Update of the 1995 Consensus Conference and the 1998 Standards, Options, and Recommendations. Ann Dermatol Venereol. 2005;132(12 Pt 2):10S3-10S85.

[31] Osella Abate S, Savoia P, Cambieri I, Salomone B, Quaglino P & Bernengo MG. Role of RT-PCR tyrosinase detection in the monitoring of patients with advanced metastatic melanoma. Melanoma Res 2000; 10(6), 545-555.

[32] Osella-Abate S, Quaglino P, Savoia P, Leporati C, Comessatti A & Bernengo MG. VEGF-165 serum levels and tyrosinase expression in melanoma patients: correlation with the clinical course. Melanoma Res 2002; 12(4), 325-334.

[33] Osella-Abate S, Savoia P, Quaglino P, Fierro MT, Leporati C, Ortoncelli M & Bernengo MG. Tyrosinase expression in the peripheral blood of stage III melanoma patients is associated with a poor prognosis: a clinical follow-up study of 110 patients. Br J Cancer 2003; 89(8), 1457-1462.

[34] Piris A, Mihm MC Jr & Duncan LM. AJCC melanoma staging update: impact on dermatopathology practice and patient management. J Cutan Pathol. 2011; 38(5):394-400.

[35] Poo-Hwu WJ, Ariyan S, Lamb L, Papac R, Zelterman D, Hu GL, Brown J, Fischer D, Bolognia J & Buzaid AC. Follow-up recommendations for patients with American Joint Committee on Cancer Stages I-III malignant melanoma. Cancer 1999; 86:2252-2258.

[36] Quaglino P, Borgognoni L, Bottoni U, Calvieri S, Carli P, Catricalà C, Eibenschutz L, Manganoni A, Moretti S, Pellacani G, Pimpinelli N, Seidenari S, Bernengo MG. Italian guidelines for staging and follw-up of stage I-I cutaneous melanoma patients. G Ital Dermatol Venereol 2007; 142: 41-47.

[37] Romano E, Scordo M, Dusza SW, Coit DG & Chapman PBSite and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol. 2010;28(18):3042-7.

[38] Savoia P, Fava P, Nardò T, Osella-Abate S, Quaglino P & Bernengo MG. Skin metastases of malignant melanoma: a clinical and prognostic survey. Melanoma Res. 2009; 19(5):321-6.

[39] Savoia P, Osella-Abate S, Deboli T, Marenco F, Stroppiana E, Novelli M, Fierro MT & Bernengo MG. Clinical and prognostic reports from 270 patients with multiple primary melanomas: a 34-year single-institution study. J Eur Acad Dermatol Venereol. 2012; 26(7):882-8.

[40] Schultz ES, Diepgen TL & Von Den Driesch P. Clinical and prognostic relevance of serum S-100 β protein in malignant melanoma. Br. J. Dermatol. 1998; 138(3), 426–430.

[41] Van der Leest RJ, Liu L, Coebergh JW, Neumann HA, Mooi WJ, Nijsten T, de Vries E.Risk of second primary in situ and invasive melanoma in Dutch population-based cohort: 1989 – 2008. Br J Dermatol. 2012; Jul 3.

[42] Voit C, Kron M, Schäfer G, Schoengen A, Audring H, Lukowsky A, Schwürzer-Voit M, Sterry W, Winter H & Rademaker J.Ultrasound-guided fine needle aspiration cytology prior to sentinel lymph node biopsy in melanoma patients..Ann Surg Oncol. 2006;13(12):1682-9.

http://dx.doi.org/10.5772/55335

[43] Wang TS, Johnson TM, Cascade PN, Redman BG, Sondak VK & Schwartz JL. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. J Am Acad Dermatol 2004;51:399-405.

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