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# Follow-Up of Melanoma: A Survey of Italian Hospitals

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**Key Words**
Melanoma follow-up · Follow-up planning

**Abstract**
Follow-up is managed internally in 94% of centers and is programmed according to international guidelines in 52% of high-volume hospitals (>25 melanoma diagnoses per year); the remainder use internal guidelines; fewer low-volume centers (≤25 diagnoses per year) have internal guidelines (25%, p = 0.001). Instrumental examinations for stage III and IV disease are similar, while the examination interval changes from 3/4 months for stage III to 2/3 months for stage IV, and use of PET/CT increases from 44 to 54%. Overall, thoracic and abdominal CT is used most for follow-up in stage III (83%), while bone scintigraphy is used more commonly in low-volume centers (41 vs. 19%, p = 0.003), despite similar use of PET/CT (48 vs. 41%). Brain CT or MRI is more common in high-volume centers (63 vs. 39%, p > 0.0001), as is echography of draining lymph nodes (71 vs. 52%, p = 0.01). Hepatic/abdominal echography and thoracic radiography are used in about 50% of centers, regardless of type. In stage IV, use of bone scintigraphy is similar among groups (ca. 40%); brain CT/NMR use increases from 51 to 64% and is more common in high-volume centers (p = 0.03). Lymph node echography is more common in high-volume centers (56 vs. 39%, p = 0.03).



## Introduction

Although melanoma accounts for a small percentage of skin cancers, it is responsible for a majority (95%) of skin cancer deaths. Most metastases occur within the first 3–5 years and there is general agreement that follow-up should be more intense during this period. Follow-up schedules aim for early detection of recurrent disease and subsequent primary tumors, which improves the probability of successfully treatment by surgery or other therapies. Secondary aims include monitoring treatment and providing education and reassurance. Although the need for clinical follow-up is universally accepted, there is still much debate on follow-up duration, the frequency of visits and the value of diagnostic tests [1].

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Current recommendations suggest routine history and physical examination every 3–6 months for the first 3 years, including laboratory tests and radiographic imaging. However, the utility of these recommendations is uncertain. It is not clear how useful routine cross-sectional imaging is in the follow-up of patients with melanoma, and the best imaging technique for detecting recurrence is not known.

The rationale for including routine imaging in follow-up is to detect distant recurrences, which raises two important questions: How many more patients would be identified by imaging that would not otherwise be identified by symptoms, self-detection, or physical examination alone? Would treatment be more effective if recurrences were detected before they become symptomatic [2, 3]?

In the absence of rigorous prospective data, it seems that routine follow-up visits to a physician remain a relatively cost-effective means of following patients with stage II and III melanoma. Patient education may also increase self-detection of recurrences.

During the past few decades, several attempts have been made to arrive at an international consensus on a follow-up schedule. Most schedules are based on the risk of recurrence. Others are based on the pattern of recurrences, data on adherence to follow-up or expert opinion. The majority of detections result from history taking and physical examination and these are also the most cost-effective for patients with AJCC stage I and II melanoma. On the other hand, Garbe et al. [4] recommended blood tests and lymph node sonography as a routine follow-up investigations.

In patients with stage I and II melanoma, frequent follow-up visits are not justified by retrospective assessment of yearly recurrence risk or the results of retrospective investigations of the detection of the first recurrence. Therefore, for this population 1–2 follow-up visits per year (based on recurrence risk) combined with patient education on self-examination may be recommended. Instrumental evaluations like CT may even represent a risk for excessive radiation exposure [5–8].

No research has been done on the type of health professional who should provide follow-up care in melanoma. General surgeons, dermatologists, plastic surgeons and general practitioners are involved, and this varies by country. A retrospective, observational study of patients with melanoma registered in a Scottish database raises some interesting points [9]. Patients (n = 1,536) diagnosed with invasive primary cutaneous melanoma between 1979 and 1997 without evidence of metastasis at surgery were followed for up to 20 years. Clinical-pathological characteristics, surgical treatment and outcomes were compared for the four groups of specialist. A majority of patients (43%) were treated initially by a dermatologist, the remainder by a general surgeon (32%), plastic surgeon (17%) or general practitioner (8%). There were significant differences in the surgical treatment between dermatologists and surgeons. Survival was significantly better in the dermatologist-treated group, suggesting that dermatologists should have a central role in melanoma management. In surveillance for second primary melanoma, especially in patients with many moles or dysplastic nevus syndrome, dermatological knowledge is essential [9].

Studies on patients with AJCC stages I and II melanoma have shown that most recurrences are detected by the patient or through history taking and physical examination by the physician. This appears to be the only cost-effective type of follow-up [6, 10–12]. Screening with chest radiography or specific serum markers such as LDH, S-100 β protein and melanoma-inhibitory activity are not justified by the evidence [7, 13–16].

While it is clear that serum markers are useful – even LDH alone was part of the AJCC classification before S-100 might become universally accepted – neither LDH nor S-100 protein has prognostic value in early disease stages. In more advanced stages instead, they can be used to identify patients who need more intense follow-up and also provide feedback on response to treatment [17–19]. Detection of circulating tumor cells with molecular markers is potentially promising as a prognostic marker [20]. However, the relationship between the intensity of follow-up and survival is not currently known [21]. More prospective evidence is needed on the effectiveness of such tests.

Guidelines for asymptomatic patients can generally be divided, on the basis follow-up intensity and examinations, into intensive follow-up [21] (table 1) or minimal follow-up [4, 12, 22–28] (tables 2–5).

Follow-up schedules can vary dramatically among centers. Generally, where patients are managed by a coordinated group of specialists, staging and follow-up examinations are planned rationally, and intensity is based on disease characteristics. On the contrary, often in peripheral hospitals, patients at low risk of metastases may receive unnecessary exams that can impact on healthcare budgets. One explanation for this could be a lack of experience with treating and monitoring patients with melanoma in centers where melanoma is diagnosed less frequently. We conducted a survey of Italian hospitals to

**Table 1.** Guidelines for melanoma follow-up in Germany, where an intensive approach is used

| Stage and tumor thickness | Physical examination years 1–5 | Physical examination years 6–10 | Lymph node sonography years 1–5 | Serum S-100 protein levels years 1–5[b] | Imaging studies years 1–5[c] |
|---|---|---|---|---|---|
| I, <1 mm | 6 | 12 | none | none | none |
| I+II, >1 mm | 3 | 6–12 | 6 | 3–6 | none[d] |
| III[a] | 3 | 6 | 3–6 | 3–6 | 6 |
| IV | individualized | | | | |

[a] Stage III includes all forms of local and regional metastasis. The new AJCC stage IIC (>4 mm tumor thickness and ulceration) should be followed as stage III, since the prognosis is similar.
[b] S-100 protein is the only parameter suited for detecting recurrences.
[c] Abdominal sonography and chest X-ray or CAT, MRI or PET.
[d] Patients receiving adjuvant therapy should receive imaging studies every 6–12 months.

**Table 2.** Guidelines for stages I–III melanoma follow-up in the UK, where a minimal approach is used

| Tumor thickness | Physical examination years 1–3 | Physical examination years 4–5 |
|---|---|---|
| In situ | none | none |
| <1 mm | none/3-monthly | none |
| >1 mm | 3-monthly | 6-monthly |

**Table 3.** Guidelines for melanoma follow-up in Australia, where a minimal approach is used

| Stage | Physical examination years 1–5 | Physical examination years 6–10 |
|---|---|---|
| I | 6 | 12 |
| II | 3–4 | 12 |
| III | 3–4 | 12 |
| IV | individual | |

determine how patients with melanoma are currently managed in Italian hospitals and present our findings regarding the follow-up programs after the diagnosis and therapy of the disease at different stages.

## Methods

Briefly, a nationwide survey of clinicians responsible for the diagnosis, 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 hospitals with ≥400 beds and a proportionally stratified random sample (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 predicted 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 total sample/total Italian hospitals, and comparisons were made between high- and low-volume centers using Pearson's $\chi^2$ test and the zeta test at 95% confidence level. Detailed methods are presented elsewhere in this issue [29].

## Results

Overall, 93% of hospitals performed their own follow-up, but there are differences in the type of guidelines used. When we analyzed centers according to the number of melanoma diagnoses per year, using the median value of 25 diagnoses as a cut-off between high- and low-volume centers, we found that more high-volume centers follow international guidelines (48 vs. 25%, p = 0.001).

*Type of Specialist Performing Follow-Up*

Another important difference between the two groups of hospitals was the type of specialist performing the follow-up. We analyzed this according to AJCC stage (2001 version). Overall, a dermatologist generally monitors patients with early-stage disease (73 and 57% for stage 0 and I, respectively). When we compared these factors in high- versus low-volume centers we found 80 vs. 65% for stage 0 and 69 vs. 45% for stage I (p = 0.01 for stage I). Follow-

**Table 4.** Guidelines for melanoma follow-up in the USA, where a minimal approach is used

| Stage | Physical examination years 1–3 | Physical examination years 4–5 | Physical examination years >6 | Skin examination | Chest X-ray, LDH level and blood counts |
|---|---|---|---|---|---|
| 0 | 12 | – | – | 12 | – |
| IA | 3–12 | – | – | 12 | – |
| IB–III | 3–6 | 4–12 | 12 | 12 | 3–12 (optional) |

up in the remaining hospitals is performed by either an oncologist or a general surgeon.

Overall, follow-up for patients with stage II disease is managed by an oncologist in 76% of hospitals and by a dermatologist in 38%; however, oncologists are more likely to manage these cases in high-volume centers (87 vs. 64%, p = 0.001), while dermatologists are more likely to be in charge of follow-up in low-volume centers (52 vs. 26%, p = 0.002). There are no statistically significant differences between groups regarding follow-up of patients with stage III disease; an oncologist was most often involved in both groups. Meanwhile, for patients with stage IV melanoma, a dermatologist was responsible for follow-up in 21% of high-volume centers, compared to 6% of low-volume centers (p = 0.02), with a majority of hospitals in both groups using oncologists in this setting.

*Follow-Up Examinations*

We also surveyed the types of follow-up radiologic examinations requested in each group according to disease stage. For stage 0, we found that high-volume centers are less likely to use sonography (21 vs. 42%, p = 0.006) and chest X-ray (23 vs. 43%, p = 0.02). Sonography of the lymphatic drainage basin was requested in about 40% of patients in both groups in stage 0, but in 77% of high-volume centers and 55% of low-volume centers for stage I (p = 0.003). This difference was paralleled by more requests for CT/MRI scans of the brain in high-volume centers (19% vs. none of the low-volume centers, p < 0.0001). When considering stage II disease, sonography was requested in more high-volume centers (79 vs. 63%, p = 0.02), and bone scintigraphy was requested in fewer high-volume centers (6 vs. 26%, p = 0.005).

Follow-up procedures for patients with stage III disease differed most between groups. Lymph node sonography was indicated in 71% of high-volume centers compared to 52% of low-volume centers (p = 0.01), while more high-volume centers performed brain CT scans (63 vs. 39%, p < 0.0001). Bone scintigraphy is used in fewer high-volume centers (19 vs. 41%, p = 0.003).

**Table 5.** Follow-up intervals (months) are based on the number of years after diagnosis according to the guidelines for melanoma follow-up in the Netherlands, where a minimal approach is used

| AJCC stage | Time since primary melanoma diagnosis, years | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6–10 |
| IB | 4 | 3 | 2 | 2 | 2 | |
| IIA | 4 | 3 | 2 | 2 | 2 | 1 |
| IIB | 4 | 3 | 2 | 2 | 2 | 1 |
| IIC | 4 | 3 | 2 | 2 | 2 | 1 |
| III | 4 | 3 | 2 | 2 | 2 | 1 |
| IV | 4 | 3 | 2 | 2 | 2 | 1 |

In stage IV, the only major difference was in the number of centers using sonography (56% of high-volume centers vs. 39% of low-volume centers, p = 0.03) and brain CT scan (71% of high-volume centers vs. 58% of low-volume centers, p = 0.03) (table 6). There was also a difference in the distribution of patient educational material, with 79% of high-volume centers doing so, compared to 41% of low-volume centers (p = 0.003). More than 60% of centers performed blood tests, with no difference by stage or type of center.

*Duration of Follow-Up*

There was no substantial difference in the length of follow-up between types of center. For stage I and II a majority (43 and 45%, respectively) of high-volume centers monitor patients for 5 years; 19% monitor for 3 years. Among low-volume centers, 37% follow stage II patients for 5 years and 34% forever. Physicians are generally responsible for follow-up.

Overall, 48% of hospitals monitor stage III patients for their entire lives, 27% for 10 years and 22% for 5 years, and this is normally managed by an oncologist (86%) or der-

**Table 6.** Examinations carried out on patients with stage IV melanoma in the 90% of Italian hospitals in which examinations are tailored to disease stage; centers are grouped according to yearly melanoma diagnoses into high-volume (>25) and low-volume (≤25) centers

| | Type of center | | |
|---|---|---|---|
| | high-volume (n = 55) | low-volume (n = 59) | all (n = 114) |
| Centers in which examinations vary according to stage | 49 (89%) | 54 (91%) | 103 (90%) |
| Procedures used in centers where examinations vary by stage | | | |
| Lymph node US | 56% | 39%* | 47% |
| Hepatic and abdominal US | 54% | 43% | 49% |
| Chest X-ray | 50% | 35% | 42% |
| Chest/abdominal CAT | 83% | 85% | 84% |
| Cranial CAT or MRI | 71%* | 58% | 64% |
| PET, PET-CT | 58% | 51% | 54% |
| Bone scintigraphy | 35% | 45% | 40% |
| Blood tests | 62% | 71% | 67% |
| Mean number of examinations | 4.7 | 4.3 | 4.5 |
| Frequency, months | 2/3 | 2/3 | 2/3 |

* p = 0.03.

matologist (27%), however in 19% of high-volume centers it is a surgeon versus 4% of low-volume centers (p = 0.01).

Most centers (58%) follow stage IV patients for their entire lives, 18% for 10 years and 20% for 5 years. An oncologist is responsible for monitoring patients with stage IV disease in 94% of hospitals; however, a dermatologist performs this function in 21% of high-volume centers versus 6% of low-volume centers (p = 0.02).

*Patient Educational Material and Psychological Support*

In 94% of centers, patients with melanoma had access to telephone counseling, but only 31% of centers offer around the clock counseling, with a significant difference between low- and high-volume centers (41 vs. 21%, p = 0.001). Psychological support was available in 75% of centers and printed patient information in 46% of centers.

## Discussion

Follow-up is approached differently in different countries, based on what is considered necessary in the absence of strong evidence of a survival benefit with any specific approach. There is general agreement that patients must be monitored for at least 10 years from diagnosis, though with a cadence that may vary, keeping in mind that visceral metastases may present after several decades. Histology at diagnosis also influences follow-up: a thin melanoma may require less intense follow-up. Instrumental examinations including traditional radiology and sonography are considered first level, tomography as second level, while examinations such as PET are indicated as third level.

The appropriate monitoring equipment is present in all hospitals, therefore the most important aspect to evaluate was whether centers, regardless of size, are performing this service internally. Our finding that follow-up for early-stage disease is generally performed by a dermatologist, while an oncologist is increasingly involved with advancing disease stage, is understandable because advanced disease tends to be inoperable and an oncologist may be better prepared to manage medical therapies. Surgeons play a marginal role in follow-up in all hospitals, regardless of stage.

All of the centers monitor patients for a similar length of time, with a maximum of 5 years when diagnosed in initial stages and progressively longer with more frequent visits for advanced stages. Instead, there are statistically significant differences in the types of examinations that are used for follow-up. Cranial imaging is requested only in high-volume centers and this is likely attributable to greater experience with this kind of tumor.

For the same reason high-volume centers do not request bone scintigraphy, which is used in 41% of low-volume centers. Asymptomatic bone metastases are rare in melanoma both as primary and isolated recurrences [24], and no guidelines or research protocols suggest the use of bone scintigraphy. When there is clinical suspicion, PET/CT is the best evaluating method [30, 31]. Published data agree that CT scans are ineffective for follow-up of patients with melanoma [7, 30, 32]. However, we found that in clinical practice CT is performed in 4 of 5 centers, with no differences between centers.

US examination for staging of lymph node drainage may permit earlier diagnosis [33] and facilitate re-operation in patients who have local recurrence, after node dissection or despite a negative sentinel node biopsy [33]. Therefore, it is surprising that 49% of centers do not use US in stage III patients, when it is recommended by the Italian Medical Oncology Society guidelines and by the Italian Melanoma Intergroup. Application of US examinations for stage IV in 49% of centers is less clear; perhaps these are performed in addition to CT to obtain the best

possible sensitivity and specificity in the evaluation of lymph nodes.

In countries where the health systems are evidence-based, in the absence of clinical evidence, melanoma follow-up is based on self-examination, with the general practitioner making most of the decisions. Other countries may use a more aggressive approach. For example, follow-up in Italy may consist of intensive instrumental examinations that may not always be justified by clinical indications, in order to ensure that patients are well monitored. The costs connected with imaging examinations are considerable, both for the national health service and the hospitals, and the risk from exposure to ionizing radiation seems unjustified in stage IIIA, where prognosis is better.

In Italian clinical practice, follow-up in low-volume centers tends to be more intense than warranted by disease stage. Whether this results from less experience with melanoma or a form of protection from malpractice is difficult to determine. Clearly a randomized study of follow-up practices is needed. Oncologists and dermatologists need to collaborate on investigating the advantages and disadvantages of a more or less intensive follow-up. Such clinical trials should involve as many centers as possible to facilitate rapid transfer of findings to clinical practice.

Psychological support and medical staff availability are satisfactory in the Italian system, with somewhat greater accessibility in low-volume centers. However, printed material on the disease and treatment is scarce, particularly in the low-volume centers, indicating that an important aspect of patient care is underappreciated [34, 35]. Most recurrences are detected by the patient [36], and information about the disease is essential. Educational materials and courses are appreciated and currently more cost-effective than radiological follow-up.

## Conclusions

In the absence of rigorous prospective data, routine follow-up visits conducted by a physician remain a relatively cost-effective means of following patients with stage I and II disease, while more instrumental diagnostic tests are proposed for patients with stage III melanoma. Follow-up should be more intense during the first 3/5 years after diagnosis, when 90% of metastases manifest, however universal guidelines have not been agreed upon and we must remember that progression can occur even decades after the initial diagnosis. Patient education deserves increased attention.

Although the need for clinical follow-up is universally accepted, there is still much debate on the frequency, duration and kind of diagnostic tests to be proposed: the heterogeneity in guidelines written in a relatively homogeneous region like Europe is symptomatic of the lack of definitive policy on this topic.

## Disclosure Statement

The authors have no disclosure in relation to this paper.

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