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Research Article

# Adjuvant Treatment with Low Dose of IFNα in Patients with Melanoma

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**Abstract**

Interferon α (IFNα) is the most used adjuvant treatment in the clinical practice for melanoma (MEL) high-medium risk patients; however the use of IFNα has yielded conflicting data on Overall Survival (OS) and disease free survival (DFS) rates.

Starting from these considerations, we conducted an analysis on our MEL patients who received adjuvant IFNα therapy, in order to identify possible predictors for their outcome.

A total of 140 patients were included in our analysis. Patients with Breslow thickness ≤ 2.00 mm presented a significant longer mean DFS than patients with Breslow ≥2.01 mm ($p = 0.01$). Using no parametric Spearman's Coefficient test we found association between DFS and Breslow thickness ($p < 0.001$) and between DFS and ulceration ( $p = 0.03$).

Performing Multiple Regression test, Breslow thickness ($p < 0.001$) remained the only statistically significant predictor. From the OS analysis we found that patients with lower Breslow values ≤ 2.00 mm ($p < 0.0001$), and absence of ulceration ($p < 0.004$) showed a significant better long-terminal survival.

From the current analysis we found that actually: the use of low dose IFN is justified only for cutaneous melanoma ≤ 4.01mm that was not ulcerated; patients with Breslow ≥ 4.01 mm, in our opinion, should not carry out adjuvant treatment with low dose IFNα, because its side effects could be higher than the its benefits.

## INTRODUCTION

The therapeutic management of malignant melanoma (MEL) is one of the most problematic issues for oncologists [1]. Among solid tumors, it is one of the most refractory to medical therapy as well as radiotherapy and therefore the surgical intervention still remains the most effective treatment for MEL, but only if performed at a very early stage. In fact the 10-year overall survival (OS) is 93% for stage IA, while for stage IIC is only 39% [2]. The agent currently most used as adjuvant therapy after radical surgery for such patients at risk to progress to stage IV is interferon alpha (IFNα), which is a type of IFN mainly produced endogenously by macrophages. First schedules of adjuvant treatment for MEL patients were based on administration of IFNα at dosage of 3 million international units (MIU) for periods ranging from one to three years [3,4]. However, up to now, the most considered schedule of adjuvant treatment for MEL patients, is the one proposed by Kirkwood et al, that considers high dosages of IFN (20-10 M IU/m2 i.v and s.c) given for one year to MEL patients at stage II [3-5]. However, more recently some authors revalued the administration of adjuvant IFNα at low dosages [6].

Although different authors have previously performed randomized controlled trials and meta-analyses on the use of IFNα as adjuvant treatment in MEL patients, their studies have yielded conflicting data on the effect on overall survival rate (OS) and disease free survival rate (DFS) [7-10]. At the same time, some papers tried to characterize possible predictors that may identify patients who would or would not benefit from this treatment [11-13]. In those studies, the main purpose was to restrict the adjuvant treatment with IFNα to only the patients with high susceptibility to respond to the therapy. Starting from these considerations, we conducted an analysis on our MEL patients who have received adjuvant IFNα therapy, to identify possible predictors for their outcome.

## MATERIALS AND METHODS

### Patients and Interferon therapy

We computer-searched the clinical records of all our patients registered into our twenty years malignant melanoma (MEL) database , from January 1st 1993 to December 31st 2012, to identify patients who received low-dose Interferon-alpha-2b (IFNα) therapy, as adjuvant treatment.

All patients had localized cutaneous MEL with a Breslow thickness ≥ 1.01 mm and had previously made surgical removal of the primary cutaneous lesion according to standard surgical criteria [14] and sentinel lymph node procedure.

At the first visit in our Department, all the patients were with WHO performance status of 0 and they performed a general visit to exclude the possible presence of an autoimmune disease (such as lupus).

The following parameters were registered: demographics, anatomical localization and histological characteristics of the primary melanoma. After starting therapy the following parameters were registered: adverse events including thyroidal dysfunction, time interval between diagnosis of primary melanoma and the first metastatic event (DFS),date of death and/or last follow-up (OS).

The clinical controls and the instrumental analyses, were carried out every 4-12 months according to our scheduled follow-up [15]. During clinical controls, the following laboratory parameters were registered: complete blood count, glycaemia, creatinine, urea, cholesterol, albumin, bilirubin, lactic dehydrogenase, liver function tests, thyroid function tests and S-100.

IFNα was administered at the dose of 3 million IU (MIU) with sub cutis (s.c.) route 3 times weekly for 6 cycles of 6 months with a 1-month intervals between cycles (36-41 months).

In case of adverse events, the dose could be reduced or suspended. If necessary, antipyretics were employed to control fever and/or malaise subsequent to the administration of IFNα.

### Thyroidal evaluation

For all patients exclusion criteria from starting IFN therapy were the presence of a thyroidal dysfunction. However in all patients after starting therapy free three-iodo-thyronine (fT3), free tetra-iodo-thyronine (fT4), TSH, anti-thyreoperoxidase antibodies (anti-TPO) and anti-thyroglobulin (anti-TG) serum levels were evaluated every 3 months after during follow up.

Hyperthyroidism was defined as having TSH < 0.1mU/l, either fT4 level > 26.0 and/or fT3 > 5.5 pmol/l. Hypothyroidism was defined as having TSH level > 4 mlU/l with normal or low fT4 levels.

After the occurrence of a thyroidal dysfunction during the IFN treatment, the therapy was always discontinued and the patient was referred to the endocrinal specialist, to evaluate the possible continuation of the therapy.

### Statistical analysis

We calculated the incidence rate (IR), free survival (DFS) and overall survival (OS) in the whole group of patients and separated in subgroups according to the parameters most studied in the literature.

The incidence rate (IR) was considered as the ratio between the observed MM patients with progression and the ones without metastatic progression.

DFS was calculated from diagnosis of primary tumor to the first metastatic progression. Assuming that the effects of the predictor variables are constant over time, we used the Spearmen's coefficient between DFS and the predictive factors analyzed including thyroidal function. The following predictors were evaluated: sex (female or male), age (≤60 or ≥61 years), anatomical location of the primary tumor (axial or peripheral), Breslow thickness (1.01-2 mm or > 2 mm), ulceration (presence or absence) and thyroidal dysfunction (presence or absence) .The first four parameters are the ones used by Balch [2]. Subsequently, the independent predictors were assessed by Multiple Regression.

To estimate OS was used the Kaplan-Meier product and the log-rank test to evaluate differences between the survival curves. Patients who were lost to follow-up or who were alive at the time of last follow-up were censored at the date of their last follow-up.

A p value < 0.05 was considered statistically significant.

## RESULTS

A total of 140 patients were included in our analysis (Table 1). They were 76 (54.28%) male and 64 (45.72 %) female. Patients with age ≤ 60 were 87, while those with age ≥ 61 were 53. According to the anatomical sites, 70 patients had melanoma (MEL) on the trunk region, 3 patients on head and neck, 27 patients on superior limbs and 40 on inferior limbs. We divided the anatomical sites in axial (trunk + head/neck = 73 patients) and peripheral (upper and lower limbs = 67 patients).

Regarding Breslow thickness, 83 patients showed a Breslow thickness between 1.01-2.00 mm, 48 patients between 2.01-4.00 mm and 9 patients a Breslow thickness ≥ 4.01mm. The ulceration of the primary tumor was found in 23 patients (16.42%), while it was absent in 117 patients (83.58 %).

Analyzing AJCC stage at diagnosis, 60 patients were in stage IB, while 44 patients consisted in stage IIA, 21 patients in stages IIB and 15 patients in stage IIC.

Among treated patients, 48 (34.28%) developed a metastatic progression (Table 1). Regarding the first event of progression appeared during the follow-up, the most frequent types of metastases were lymph-nodal or in transit (n= 32) followed by (distant) dermal ones (n = 2), lung (n= 8) and brain metastases (n= 6).

After starting IFNα adjuvant therapy 10 (7.14%) patients showed thyroid dysfunction; they were 9 female and only 1 male patient. Thyroid abnormality occurred with a median time of 4.2 months after the first IFNα administration. Eight patients

developed hypothyroidism, while two patients developed hyperthyroidism (Table 2). Generally elevation or suppression of TSH level was the main sign of thyroidal dysfunction. In 8 patients specific antibodies anti-thyroperoxidase and/or anti-thyroglobulin were found (Table 2). Anti-microsomial DNA antibodies in one patient and ANA in two patients were also detected. Autoimmune diseases other than autoimmune thyroiditis, such as lupus erythematosus, were not observed. In all the patients that developed thyroidal dysfunction, these alteration was not present before starting IFNα therapy. After registering thyroidal dysfunction, IFNα therapy was temporarily suspended in 1 patient while in 2 patients IFN was reduced from 3 to 2 or 1 administration per week.

Dividing the patients according to clinical stage, the incidence rate (IR) of recurrences was 1:7 in stage IB patients, 1: 2.5 for stage IIA patients, 1:1 for stage IIB patients and 2:1 for IIC stage patients.

To identify possible predictor factors for MEL progression after adjuvant treatment with IFNα we analyzed statistically the correlation between DFS and some characteristics of melanoma tumors and patients (Table 3). Female patients showed a better DFS than male (46 years versus 27 years), althought not reaching the statistical significance ($p = 0.3$). Patients with age ≥ 61 years had median DFS of 23 months while younger patients had median DFS of 32 months ($p = 0.7$); while for patients with an axial primary localization the median DFS was 27 months, while it was 31 months for peripheral localization ($p = 0.3$) . Patients with Breslow thickness ≤ 2.00 mm presented a significant longer median DFS than patients with Breslow ≥ 2.01 mm ($p = 0.01$); Patients with ulcerations showed median DFS of 21 months while it was 44 months for patients without ulceration ( $p = 0.2$). In patients with thyroidal dysfunction median DFS was 44.5 months while for patients without a thyroidal dysfunction was 24 months ( $p = 0.3$) (Tabel 3).

Using no parametric Spearman's Coefficient test between DFS and the single variables, we found association only between DFS and Breslow thickness ($p < 0.001$; Spearman's coeff = 0.409) and between DFS and ulceration ( $p = 0.03$; Spearman's coeff = 0.284). Performing Multiple Regression test, Breslow thickness ($p < 0.001$) remained the only statistically significant predictor (Table 3).

Subsequently we analyzed OS of the patients using Kaplan-Meier product and log-rank test according to variables previously described: gender, age, sites of primary tumor, Breslow thickness, ulceration, thyroid dysfunction. From the OS analysis we found that patients with lower Breslow values ≤ 2.00 mm ($p < 0.0001$), and absence of ulceration ($p < 0.004$) showed a significant better long-terminal survival Table 3 and Figure 1a-1b). Regarding OS in patients with and without thyroid dysfunction, Kaplan-Meier curves showed, during the first 2 years of follow-up the same behavior, while in the longer follow up patients with thyroidal dysfunction showed better OS, however without reaching the statistical significance: 71 months versus 64.4 months with $p = 0.2$ (Figure 2).

Subsequently, we analyzed the number and type of melanoma

**Table 1:** Characteristics of melanoma patients that underwent to IFNα therapy. *yrs* indicates years.

| | | |
|---|---|---|
| **Gender** | Male<br>Female | 76<br>64 |
| **Age** | ≥ 61<br>≤ 60 | 53<br>87 |
| **Anatomical Sites** | Central<br>(Trunk – Head/neck)<br>Periferal<br>(Superior Limbs - Inferior Limbs) | 73<br>(70 – 3)<br>67<br>(27-40) |
| **Breslow thickness** | T2 (1.01-2.00 mm)<br>T3 (2.01- 4.00mm)<br>T4 ( > 4.01mm) | 83<br>48<br>9 |
| **Clark level** | II<br>III<br>IV<br>V | 2<br>55<br>75<br>8 |
| **Ulceration** | Presence<br>Absence | 23<br>117 |
| **AJCC classification** | IB<br>IIA<br>IIB<br>IIC | 60<br>44<br>21<br>15 |
| **Disease Progression** | Presence<br>Absence | 48<br>92 |
| **First metastatic site** | Lymph nodal and in transit<br>Dermal (distant)<br>Lung<br>Brain | 32<br>2<br>8<br>6 |
| **Thyroidal dysfunction** | Presence<br>Absence | 10<br>130 |

**Table 2:** Thyroid dysfunction in patients after treatment with IFNα.

| Patient | fT3 | fT4 | TSH | Ab-TPO | Ab-Tg | Thyroid dysfunction |
|---|---|---|---|---|---|---|
| **1** | N | N | ↑ | ↑ | N | thyroiditis with hypothyroidism |
| **2** | N | ↓ | ↑ | ↑ | N | thyroiditis with hypothyroidism |
| **3** | N | N | ↑ | ↑ | ↑ | thyroiditis with hypothyroidism |
| **4** | N | N | ↑ | ↑ | ↑ | thyroiditis with hypothyroidism |
| **5** | N | ↑ | ↓ | N | N | hyperthyroidism |
| **6** | N | N | ↑ | ↑ | N | thyroiditis with hypothyroidism |
| **7** | N | N | ↑ | ↑ | N | thyroiditis with hypothyroidism |
| **8** | N | ↑ | ↓ | N | N | hyperthyroidism |
| **9** | N | N | ↑ | ↑ | N | thyroiditis with hypothyroidism |
| **10** | N | N | ↑ | ↑ | N | thyroiditis with hypothyroidism |

**Table 3:** DFS and OS in patients under treatment with IFNα ;statistical analysis.

| | DFS (median months) | $p^a$ | $p^b$ | $p^c$ | OS (median months) | $P^d$ |
|---|---|---|---|---|---|---|
| **Gender**<br>**Male**<br>**Female** | 27<br>46 | 0.3 | 0.7 | 0.7 | 53.6<br>76 | 0.6 |
| **Age**<br>**≥61**<br>**≤60** | 23<br>32 | 0.7 | 0.8 | 0.9 | 57<br>68 | 0.4 |
| **Sites**<br>**Axial**<br>**Extremities** | 27<br>31 | 0.1 | 0.5 | 0.1 | 48<br>82 | 0.06 |
| **Breslow**<br>**≥ 2.01 mm**<br>**≤ 2.0 mm** | 23<br>84 | *0.01* | *<0.001* | *<0.0001* | 50<br>74.2 | *< 0.0001* |
| **Ulceration**<br>**Presence**<br>**Absence** | 21<br>44 | 0.2 | *0.03* | 0.1 | 38<br>71 | *< 0.004* |
| **Thyroid dysfunction**<br>**Presence**<br>**Absence** | 44.5<br>24 | 0.8 | 0.3 | 0.9 | 71<br>64.4 | 0.2 |

$p^a$ readapted log-rank test to DFS; $p^b$ Rank correlation and Spearman's coefficient between DFS median time and predictors; $p^c$ Multiple Regression analysis between DFS median time and independent predictors; $p^d$ Kaplan- Meier product and log-rank test among OS median time and predictors. In italic, significant values.

metastases according to the initial AJCC stages (IB; IIA; IIB and IIC), to better evaluate the predictive activity of disease staging. We found a higher incidence of metastases in stage II patients; they were 38 divided as follow: 12 for patients in stage IIA, 14 for stage IIB and 12 for stage IIC. In details patients in stage IIC developed lymph node or in transit metastases in 9/15 cases, lung metastases in 1/15 case, brain metastases in 1/15 cases while only in 4 patients melanoma did not progress (Table 4). Another important finding, is the relative presence of lung metastases also in patients with low-intermediate stages (IB and IIA). (Table 4)

Regarding 5-years-OS and 10-years-OS (Table 4), dividing the patients according to stage, we found for stage IB 5-years-OS of 98% and 10-years-OS 95%; while regarding stage IIA 5-years-OS was 85% and 10-years-OS was of 78%. For stage IIB 5-years-OS was 80 % and a 10-years-OS of 65%, while for stage IIC 5-years-OS was 50% and 10-years-OS was 25%. Confronting these data with the data from Balch et al. [16] regarding patients at the same stage of disease we found that for our patients in stage IB IIA and IIB the 5-years-OS and 10-years-OS were better than the ones reported by Balch et al. [16] while for stage IIC the data were similar or worse (Table 4). Finally we analyzed DFS and OS of our patients regarding the first type of melanoma metastasis. We found that patients with lymph nodal and in transit metastases had median DFS of 30 months and median OS of 117 months while patient with distant dermal metastases had median DFS of 20 months and median OS of 72 months, lung metastases showed median DFS of 27 months and median OS of 48 months and brain metastases median DFS of 40 months while median OS was 44 months (Table 5). Among patients with a peripheral involvement, 9 patients showed an acral malignant melanoma.

## DISCUSSION

Among the available treatment options for malignant melanoma (MEL), surgical resection,with or without regional lymph node excision, represents the standard of care and allows regional control of the disease and improves survival [8].

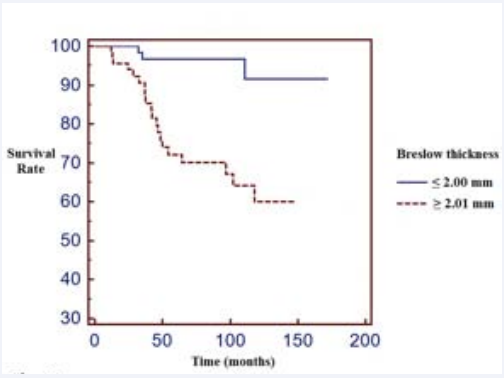


**Figure 1a** Overall survival of melanoma patients treated with IFNα adjuvant therapy according to Breslow thickness ( ≤ 2.00 mm or ≥ 2.01mm).

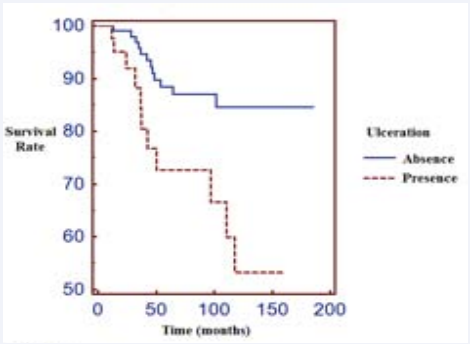


**Figure 1b** Overall survival of melanoma patients treated with IFNα adjuvant therapy by the presence or absence of ulceration in primary cutaneous melanoma.

**Table 4:** Types of metastases and 5-years and 10 years OS of patients under treatment with IFNα according to initial melanoma stage. Comparison of our casistics with those of Balch et al.[16].

| *STAGE* | *#pts* | *#pts met* | *regional lymph node and in transit met* | *distal skin* | *lung* | *brain* | *5-year-OS (our casisitics)* | *10-year-OS (our casistics)* | *5-year-OS (AJCC casisitics)* | *10-year-OS (AJCC casistics)* |
|---|---|---|---|---|---|---|---|---|---|---|
| **IB** | 60 | 8 | 5 | 1 | 2 | - | 98 | 95 | 89.8 | 81.1 |
| **IIA** | 44 | 13 | 6 | 1 | 3 | 3 | 85 | 78 | 78.2 | 64.1 |
| **IIB** | 21 | 16 | 12 | - | 2 | 2 | 80 | 65 | 65.2 | 52.4 |
| **IIC** | 15 | 11 | 9 | - | 1 | 1 | 50 | 25 | 45.1 | 32.3 |

#pts indicates number of patients; met indicates metastases

**Table 5:** DFS and OS in patients under treatment with IFNα according to the first event of progression (metastasis).

| Metastases | *n* | DFS (median months) | OS (median months) |
|---|---|---|---|
| **Lymph Node and in transit** | 32 | 30 | 117 |
| **Dermal (distant)** | 2 | 20 | 72 |
| **Lung** | 8 | 27 | 48 |
| **Brain** | 6 | 40 | 44 |

*n* indicates number of patients; DFS indicates disease free survival; OS indicates overall survival.

However for patients with high risk (stage IIIB and resectable stage IV M1a and M1b) and also with intermediate risk (stage IB-II and IIIA) adjuvant treatment seems advisable. For this purpose most international trials have used Interferon–alpha 2b (IFNα) as adjuvant treatment.

However, the use of IFNα has yielded conflicting data on the effect on Overall Survival (OS) and disease free survival (DFS). In fact, in a recent Meta-analysis, Mocellin et al. registering inappropriate statistical models and contrasting results among different studies with IFNα as adjuvant treatment, concluded that more efforts are necessary to identify patients who could have benefit from IFNα adjuvant therapy [6,17].

Starting from this point of view (6) we performed this retrospective study. Participating to a spontaneous Italian multicenter protocol, we administered to our melanoma patients with Breslow's depth > 1 mm as adjuvant treatment IFNα at 3 million international units (MIU) 3 times per week for 6 cycles of 6 months each one. MEL at stage III received other adjuvant treatment with dacarbazine with or without IL-2 and in some cases IFNα at higher doses as suggested by Kirkwood et al [3-5].

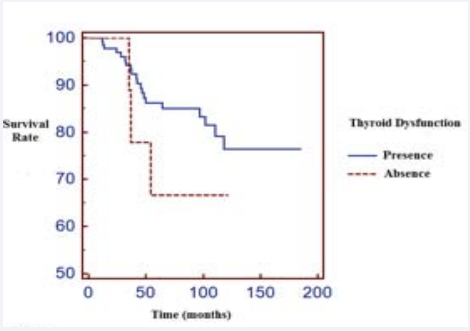


**Figure 2** Overall survival of melanoma patients treated with IFNα adjuvant therapy by the presence or absence of a thyroidal dysfunction, arose during the therapeutic treatment.

To put in evidence any characteristics of patient or MEL useful to identify people more susceptible to adjuvant treatment with IFN, first we analyzed DFS and OS of our patients according to the same prognostic factors as the ones studied by Balch et al. to establish melanoma staging (2).These parameters were: sex, age, anatomical site of first melanoma lesion, Breslow thickness, ulceration. Using the readapted log-rank test for DFS (Tabel 1),

the only significant predictors were Breslow thickness ( p = 0.01) and ulceration (p < 0.03). Performing Sperman's test, again low Breslow thickness (p < 0.001) and absence of tumor ulceration (p = 0.03) resulted the principal and significant values, while in the multiple logistic regression, Breslow thickness (p < 0.0001) remained the main predictor. Our results were similar to those reported in other reports [18-20].

Regarding OS analysis confronted to the same prognostic factors, we observed that low Breslow (p <0.0001) and absence of ulceration (p < 0.004), were the principal statistical values to determine a better long-term OS. However as we reported in other studies Kaplan Meyer' products (Figure1a and Figure 1b) show that Breslow thickness is more important for the first 2-5 years of follow up ulceration of the melanoma is negative prognostic factor above all for the following years. In fact,ulceration it is known that it is a marker of an increased propensity for hematogenous dissemination and extracellular matrix invasion independently by tumor thickness [21,22].

However if these data confirm that our groups of patients are similar to other groups reported in the literature namely the ones used by Balch et al. (2) to establish AJCC classification for MEL, they do not help us to identify patients more susceptible to receive adjuvant treatment with IFNα.

Therefore, according to some data of literature, we analyzed the outcome of MEL patients with thyroid dysfunction induced by IFNα. This event is regarded as a direct immune modulatory action of the drug on the patient immune system. We must highlight that according to our protocol all the patients before starting adjuvant treatment with IFNα were analyzed to exclude a pre-existing thyroid dysfunction. Therefore our patients that developed thyroid dysfunction after starting IFNα therapy must be regarded as the ones with an immuno-responsivity to IFNα administration. Interestingly patients that developed a thyroidal dysfunction showed DFS values better than the ones without thyroid dysfunction but the statistical significance was not reached (p= 0.3). In fact in patients with thyroidal dysfunction median DFS was 44.5 months about twice the median DFS (24 months) observed in patients without thyroidal dysfunction. Regarding OS and thyroid dysfunction (Figure 2) we observed that during the first 2-3 years it was not important while in the following years people with thyroid dysfunction presented better results than the one without. On considering that most patients with thyroid dysfunction were affected by autoimmune thyroiditis, we highlight that, in literature, autoimmune disorders, spontaneous or induced by IFNα, have been associated with improved prognosis in MEL and no-MEL patients ( such as patients with hepatitis C) [23-29]. However conflicting data are still reported in literature and the predictive value of autoimmunity still needed to be elucidated; in fact, while autoimmunity remains a strong independent prognostic marker in Gogas et al. [30] it is not considered in the EORTC 18952, Nordic IFNα and ECOG 2696 [31].

Again these results do not help to identify patients who could achieve more benefit from IFN therapy. Therefore we revised critically the number and type of metastases for each MEL stage and for each one we verified 5-years-OS and 10-years-OS, similarly to what reported by Balch et al. establishing AJCC staging for MEL [16]. Stressing on 5 and 10 years OS, dividing patients according to the relative AJCC stages, we found better OS in IB patients if compared with larger but similar data reported by Balch et al. (16). This increased OS was maintained also for IIA stage, but was stable or decreased for stages IIB-IIC. At the same time we registered high percentage of lymph node metastases in stage IIB-IIC. This fact confirms the hypothesis, stated by some authors, that in this class of patients ( pT3a-pT4b) a lymphadenectomy, regardless of the sentinel lymph node status, should be taken into account. In this way, an elective lymphadenectomy could replace a treatment with IFNα, which in in the current study as in other studies did not find significant improvements [32-34].

Finally we analyzed DFS and OS according to the type of first metastasis. The number for each group are not large but anyway they suggest that in these patients loco-regional metastases are not rare, are more early than brain metastases but they often permit a better prognosis for OS, while brain metastases, as we reported in another study, are more late but they not permit a long OS.

Summarizing, from the current analysis come out four principal points : i) the use of low dose IFN is justified only for cutaneous melanoma ≤ 4.01mm not ulcerated; ii) although there is a better DFS and OS in patients with thyroidal dysfunction, a statistical significance is not reached; iii) patients with Breslow ≥ 4.01 mm should not carry out adjuvant treatment with low dose IFNα, cause side effects could be higher than the benefits; iv) a radical lymphadenectomy can be considered a standard procedure for melanoma patients at stage ≥ pT3a.

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