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Melanoma in Pediatric, Adolescent, and Young Adult Patients

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Abstract

The family practitioner, pediatrician, and dermatologist each have potential roles in the primary prevention, diagnosis, and treatment of localized thin melanomas. Surgical and medical oncologists are often involved when controversy arises over the nature of the skin lesion or whether sentinel lymph node (SLN) biopsies and adjuvant therapy are to be contemplated. This overview of melanoma will deal with the primary and nodal pathology, surgery, and medical therapy of melanoma in pediatric, adolescent, and young adult patients—and will raise areas of controversy that are only recently being addressed in databases of cases from this age group.

Introduction

In the United States, melanoma is the sixth most common cancer in men and seventh most common cancer in women (1), resulting in more than 62,000 cases annually (2). In California, one of the largest states, melanoma is the second most common incident cancer in persons under 40 (3). A recent analysis of California Surveillance Epidemiology and End Results (SEER) data investigated outcome differences in younger patients compared to older ones for invasive cutaneous melanoma. The analysis found that when malignant melanoma presented as a localized lesion in younger patients, which accounts for nearly 80% of such cases, the five-year overall survival (OS) exceeds 90%. However, while the prognosis for patients with thin malignant melanoma is generally excellent, it still accounts for approximately 10% of melanoma deaths in this population. In contrast, the five-year OS for regional disease is 65% and is only 15% for distant metastatic disease (4).

It has been shown previously that adolescent and young adult patients (AYAs) can withstand intensive treatments and resemble pediatric patients more than adults in this regard.⁵ Lower rates of medical comorbidities and polypharmacy, as well as other factors, may permit AYAs

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to tolerate higher agent doses and toxicity than older patients.⁶ This is especially important for therapies that are optimized at the highest-dose treatment levels, including biological agents known to be of benefit in melanoma—such as high-dose IL-2 and high-dose IFN α -2b. Despite this, unfortunately, AYAs continue to be treated under guidelines that were created for and studied primarily in older adults, so it is possible that AYAs may be under-treated relative to their tolerances.⁶ Whether this has led to any systematic compromise of their outcomes is presently unknown.

Despite the growing awareness of potential distinct physiological characteristics for this group, AYA participation rates in clinical trials is drastically lower than that for pediatric patients and also lower than that for adults in general.⁷ While they may be included in the eligible age range (the AYA group is formally defined by the National Cancer Institute as those aged 15–39), few studies have analyzed and reported results for AYAs. A preliminary survey of the literature demonstrates that few trials have enough AYA participants to have the statistical power to allow analysis stratified by age and even large trials often omit analyses within this age range.

Biopathology of Melanoma in The Pediatric, Adolescent, and Young Adult Populations

The biopathology of melanoma among pediatric and young adult patients has been the subject of controversy. Many texts maintain that “melanoma is melanoma.”⁸ From the standpoint of pathology, while it is true that there are both clinical and pathological similarities among melanomas, there are well-known exceptions (e.g., malignant blue nevus, ‘animal’ type melanomas) which do not exhibit usually encountered features—such as prominent atypia and varying degrees of upward (Pagetoid) spread. The basic criteria for the diagnosis of melanoma have changed little from the time of Unna.^{9–13}

In pediatric and AYA patients, a subgroup of melanocytic neoplasms that is increased in frequency and of considerable difficulty is the spindle and epithelioid, or Spitzoid, melanocytic neoplasms. Indeed, in 1989 and 1992, a group from Armed Forces Institute of Pathology instituted the term ‘metastasizing Spitz nevus,’^{14,15} which, due to the identification by a biologic potential (if it metastasizes, it is melanoma), became synonymous in later years with a type of malignant melanoma with Spitz nevus-like cytology, later deemed a Spitzoid melanoma. The entity known as Spitz nevus was first described by Sophie Spitz in 1948,¹⁶ denoting these as “melanomas of childhood.” Clinically, these lesions present as benign, small, and asymptomatic superficial skin tumors that are dome-shaped and usually pink or tan, but also sometimes brown or black. Pathologically, these melanocytic nevi have spindle and epithelioid cell cytology exhibiting epidermal hyperplasia, zonation (a term used to indicate that the cytologically similar cells in the lesion tend to group together), Kamino bodies (dull pink globules), giant cells (melanocytes) at the dermo-epidermal junction, loss of cohesion of nests, junctional cleavage, and various degrees of pagetoid (upward) spread in the epidermal component.

Although the criteria for the diagnosis of melanoma and Spitz nevi have evolved over the years, the key features articulated nearly 20 years ago remain useful¹⁷ and are summarized in Table 1 below.

Additional criteria, including ‘consumption’ of the epidermis,¹⁸ have been utilized in diagnosis that are felt to represent impending ulceration. Some of these features include thinning of the epidermis with attenuation of the basal and suprabasal layers and a loss of rete ridges in areas of direct contact with neoplastic melanocytes.

Cerroni et al.¹⁹ identified and outlined the difficulties in diagnosis, including that some banal lesions that appear as Spitz nevi are found at the regional nodal station and that firm criteria for differentiation of these entities are still lacking. They also felt that additional techniques, such as molecular pathology or sentinel node biopsy, might need to be employed in further evaluation of these lesions.¹⁹

Pathologically speaking, the problem often arises from the fact that incomplete biopsy (sampling) will lead to the evaluation of the most atypical portion of the process—the superficial part, where cytologic atypia, pagetoid spread, and mitoses are more prominent, while the deeper component and lesion where maturation, symmetry, and other features of benignity are to be seen in a fuller and more complete biopsy. When specimens are processed by laboratories inexperienced with melanocytic lesions, embedding artifacts and margins that are not evaluable become issues, in association with difficulties in assessing orientation. It is not uncommon that a biopsy of such a lesion undergoes several second (expert) reviews, which may add to the diversity of opinion.

To compound this problem, some have tended to term lesions that cannot be classified as benign beyond doubt as melanoma,^{20–22} which may fail to recognize that these lesions in the young may not follow the prior adult paradigms of Clark's or Breslow's prognostic models. This has resulted in the origin of an entity known as 'melanocytic tumor of uncertain malignant potential' (MELTUMP); Spitzoid features are common in this group of lesions. In the work of Barnhill et al., the inclusion criteria for study required a definitive clinical outcome on each of the patients entered into the study; each case was reviewed independently and blindly by 10 pathologists. A clear consensus was not possible to reach in 17 cases (56.7%). In only one case did six or more pathologists agree on a category, regardless of clinical outcome. Based on these results, the group outlined the lack of criteria that would allow a distinction of benign melanocytic lesion from melanoma and histopathologic criteria to gauge the malignant potential of these lesions.²³

Spread of the neoplasm to the regional lymph node basin is at least one aspect that is generally accepted as beyond the banal or typical Spitz nevus.^{24–29} Among 71 patients summarized in these reports, 25 patients (35%) had experienced spread to at least one sentinel node and four had one or more additional lymph nodes involved at the time of completion dissection (5.6%), representing 16% of patients with a positive sentinel lymph node. Clinically, among the lesions originally reported by Spitz, only one of 13 cases demonstrated fatal outcome (7.7 %), leading her to conclude that "There is some evidence that even though metastasis may occur in childhood, an inhibitory factor may exist before puberty to hinder either further dissemination or reception of metastatic cells by the viscera..." and "A generally appreciated feature...was the lack of correlation between the depth...of the lesions and the ultimate outcome." Dr. Spitz concluded that "Accordingly...conservative surgery, rather than radical surgery usually indicated for adult melanomas, seems justified."¹⁶ The literature now includes more than 100 cases of Spitzoid neoplasms that have metastasized to loco-regional lymph nodes; much more attention is given to their pathology than cases of metastatic basal cell carcinomas, which may be several times more numerous.³⁰

Molecular techniques such as comparative genomic hybridization (CGH) have gained momentum in the investigation of these neoplasms. Although a detailed overview of this technology is beyond the scope of this article, it suffices to note that CGH is a method that allows for genome-wide detection of DNA copy number changes, comparing the neoplastic genome to the normal genome and allowing for detection and mapping of genomic aberrations that result in changes in DNA copy number. Since CGH can be performed on paraffin embedded fixed tissue samples and represents the outcome for averages of the entire cell populations analyzed, fine genomic disturbances such as balanced translocations and point

mutations are not detectable using this technique, as these events do not result in DNA copy number changes. CGH has been applied to melanocytic neoplasms of Spitzoid morphology by Boris Bastian et al., resulting in the finding that over 95% of the melanomas analyzed had multiple chromosomal aberrations, whereas the majority of nevi analyzed had either no aberrations or a very restricted set of aberrations that showed little overlap with melanoma. Spitz nevi (typical, without concerning features) did not reveal more than an isolated gain in the region of chromosome 11 (11p). Recurrent Spitz nevi revealed higher frequencies of 11p gain, which was in sharp contrast with melanomas that revealed multiple other chromosomal abnormalities. The nevi that revealed an increase in 11p also showed frequent mutations in the gene encoding H-RAS (67%) and were larger and predominately intradermal, with Spitz-like cytology and morphology.³¹

More recent work has revealed that Spitz nevi lack the BRAF mutations that are common in melanocytic nevi and melanomas.³² Spitz nevi as a group show high levels of p16 expression. By comparison, BRAF mutations are detected in 29% of melanomas and 21% of melanocytic nevi with non-spitzoid morphology.^{33,34} The value of assessing mutations in the BRAF, N-RAS, and H-RAS genes to distinguish Spitzoid melanoma from Spitz nevus is not established for lesions of pre-pubescent melanocytic lesions,³⁵ where in some cases the diagnosis of melanoma is considered synonymous with sentinel lymph node involvement.^{36,37}

In summary, there are marked differences between the patterns of melanomas and melanocytic nevi, where neoplasms of Spitzoid morphology commonly seen in younger patients and the genetic differences may be exploited for the differential diagnosis of these melanocytic tumors where histopathologic assessment is indeterminate. The role of p16 and the presence or absence of BRAF lesions may allow an understanding of the prognosis of these lesions as larger series with adequate follow-up and molecular assessment become available.

Surgery

To date, the surgical care of pediatric, adolescent, and young adult melanoma has been extrapolated from the results in prospective randomized trials for adults. There have been no similar studies of magnitude in children. For the young with melanoma, controversy arises regarding surgical and subsequent medical therapy due to the increased proportion of neoplasms in which the biological behavior of the melanocytic process may differ compared to outright melanoma, as discussed in the PATHOLOGY section above. The rationale for and interpretation of SLN biopsy results may not apply directly from the adult population to the melanocytic lesions of the young. In this section we will outline current surgical care and discuss the controversial areas of surgery for which reasonable recommendations based on current data may be made.

For patients under 30 years of age, in general, any melanoma equal to or greater than 1 mm in Breslow's thickness should be treated by wide local excision with a margin of 2 cm. For those melanomas between 1 and 2 mm, within reason and with good judgment it is acceptable to perform an excision with margins of 1–2 cm, especially when limited by vital or cosmetically sensitive areas such as the eye or lips. For those melanomas under 1 mm, a 1 cm margin is recommended as reasonable. *In situ* melanomas require a clear margin, with the recommendation of 5 mm with a 'cuff' of subcutaneous tissue. All invasive melanomas should have the wide local excision margins taken down to the muscle fascia beneath the lesion, to include all subcutaneous tissue corresponding to the 1 or 2 cm margin area.^{38,39}

Controversy arises in the recommendation for sentinel lymph node biopsy and the interpretation of SLN biopsy in children and young adults. Based on the results of the large data review performed for the 6th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, there is not a strong indication to perform SLN biopsy for melanomas less

than 1 mm in thickness (thin melanoma, stage IA).³⁸ Melanoma of stage IB is currently defined by the presence of one or more adverse factors, such as a Clark's level of IV (reticular dermal invasion) or ulceration of the epidermis. Additionally, patients with incomplete ('shave') biopsies that are positive at the deep margin should be counseled to seek SLN biopsy. For these younger patients, if there are one or more mitoses reported per square millimeter, there is a greater likelihood of a positive SLN.^{40,41} In addition, the closer a melanoma approaches 1 mm in thickness and as ulceration is apparent in the primary lesion, the more one should recommend SLN biopsy, in both young and older patients. The data that supported Clark's level IV as a threshold that would indicate high enough likelihood to warrant recommendation of SLN biopsy has been downplayed in the current analysis of data for the 7th edition of the AJCC Melanoma Subcommittee.⁴²

Indeed, it is expected that in the 7th edition of the AJCC staging manual, Clark's levels will be supplanted by mitotic index and only used when the evaluation of mitotic index is confounded or unavailable. The likely future threshold of discrimination between T1a and T1b will henceforth depend upon mitotic activity and the presence of at least 1 mitosis/mm² to argue for the pursuit of SLN biopsy staging. The data relating to the number of mitoses/mm² show the correlation of mitotic rate to SLN positivity reveals an inverse relationship to the patient's age and is directly proportional to the number of mitoses/mm².^{40,41,43,44} Therefore, SLN biopsy is recommended for patients under 30 with a thin melanoma that is ulcerated or has a mitotic rate greater than or equal to 1/mm². For patients with a melanoma under 0.76 mm in thickness, data less clearly argue for SLN biopsy. In these instances, discussion with the pediatric and adolescent patients and their family members is required. Certainly other characteristics of a melanoma, such as perineural and lympho-vascular invasion and the absence of a host lymphocytic response, and the presence of features of regression may shape decision and influence the recommendation for SLN biopsy. The use of histopathologic evidence of regression has become tenuous for decisions regarding SLN biopsy. In the past, data suggested an increased likelihood of recurrence with regressed primary melanomas, but the data collated for the AJCC 7th edition has suggested a more favorable connotation of regression, but one is insufficient to warrant inclusion in the staging system at this time.⁴⁵

The next question for surgical treatment concerns what benefit is gained from completion lymph node dissection (CLND) in pediatric and AYA patients with melanoma and a positive SLN. No prospective randomized data yet allow us to address this question. In addition, whether younger patients with a positive SLN may fare better than their adult counterparts is uncertain. SEER data analyses done by Strouse, Hamre, and Pappo's groups argue that there is little difference between the survival outcome of adult and pediatric populations with regional nodal metastasis.⁴⁶⁻⁴⁸ Anecdotal reports suggest that melanomas in the pediatric age group may be aggressive with more atypical features.⁴⁹ Lange et al. showed that the overall survival of patients aged 1-9 was worse than for aged 10-24 and that male patients aged 10-24 had a worse outcome than females in this age group. Oddly, in patients aged 1-19 with localized invasive melanoma, survival was not correlated with primary tumor thickness.⁵⁰ Roaten et al. have reported a 40% rate of positive SLN in pediatric melanoma patients 12-20 years of age (some with atypical Spitz nevi); no recurrences were documented in this population over a median follow-up interval of 35 months, compared to an 18% incidence of positive SLN and 25% recurrence rate with 9.1% mortality among adults studied in parallel for a median of 17 months ($p = 0.01$).^{51,52} Livestro et al. reported a rate of positive SLN in 18 patients under 21 years of age that was 50%, with an average primary tumor thickness of 2.9 mm among study patients.⁵³ OS appears improved among the young compared to patients below and above 21 years of age, but these differences were not statistically significant (five-year cause-specific survival for those < 21 = 91.3% and for those ≥ 21 = 86.2%; mean age 17.2 years vs. 53.8). They did not directly correlate the presence of a positive SLN with survival but showed that tumor-involved lymph node status was a negative prognostic factor in relation to melanoma-

specific survival. Survival in younger melanoma patients with positive SLNs was not as good in reports by Bütter et al. (75% for stage III).⁵⁴ Toro et al. reported three out of 12 patients with positive SLN biopsy who underwent CLND, among which one had further micrometastatic nodal disease found upon CLND and recurrence 6.1 months later before dying with hepatic metastasis at 7.5 months. All remaining 11 patients were alive and disease-free at 11.7 months of follow-up.⁵⁵ Clearly however, there is reasonable data to support finding a greater number of positive SLNs in younger patients, especially if correlated to the mitotic rate of the primary tumor.^{40, 41, 43, 50, 51, 53}

The impact of a positive SLN on the survival of pediatric and young adult patients is not well documented; as such, the standard of care should parallel that of adults with CLND for any basin in which a SLN is positive. It is evident that there are subsets of patients in which CLND has an elevated yield.⁵⁶ Based on the Multicenter Selective Lymphadenectomy Trial (MSLT-I), patients with positive SLNs who undergo CLND are expected to have improved disease-free survival (DFS) compared to patients who are simply observed (although this study was underpowered to detect the small improvement in melanoma-specific survival.⁵⁷ Based on one large recent study of matched patient SEER data, survival appears to be improved in patients that have had an SLN biopsy and treatment.⁵⁸

A further area of controversy revolves around Spitz nevi, atypical Spitz nevi, and melanocytic lesions of uncertain malignant potential (MELTUMPs), already discussed from the pathological vantage. What margins of excision should ultimately be suggested for these patients? Which lesions have malignant potential and the capacity for distant spread and lethality? Can we distinguish melanomas that will behave aggressively from a setting in which a metastasis to the regional lymph node is not a biological marker of aggressiveness? SLN biopsy status appears to be a critical discriminant of the biological behavior of melanoma in adults, and no compelling data allow us to dismiss the appearance of melanoma in the regional lymph node of pediatric and young adult populations at this time. CLND in patients with a positive SLN is therefore reasonable for the prognostic assessment of patients with a primary lesion > 1 mm, or in consideration for any melanoma with ulceration or a deep margin positive on initial partial 'shave' biopsy—as is often the case for biopsies taken in the pediatric and young adult populations, as noted above. Is there a continuum of risk that can be identified? Some dermatopathologists argue that lesions described as MELTUMP should be reported as Spitz nevi, benign nevus, or melanoma. They believe we will gain a better understanding of melanocytic tumor behavior by avoiding the use of a MELTUMP diagnosis as larger databases are collected and as we gain longer patient follow-up in the sentinel node era.⁵⁹

The controversy now in the literature with respect to the above questions cannot be answered absolutely and with certainty. There are no prospective randomized trials to address these issues and the retrospective literature is comprised of small studies with variable results and biases.

As noted in the PATHOLOGY section, five studies have reported on 71 patients with sentinel lymph node biopsies for diagnostically difficult Spitzoid tumors.^{25–29} In these studies, 26 (36.6%) out of 71 patients with atypical Spitz tumors who underwent sentinel lymph node biopsy had positive nodal melanocytic aggregates.^{24, 60} No histological or clinical features distinguished the node-positive and negative groups apart from Breslow's thickness.^{25–29} Even so, recurrence and survival rates in these studies are variable and SLN biopsy and CLND were not uniformly pursued. The high rate of sentinel lymph node positivity among younger patients poses a central paradox given the suggestion of improved prognosis for younger patients with regional lymph node involvement. Biological differences in tumors of pediatric and young adult populations suggest that 'metastasis' may be less ominous. A great deal of controversy exists in regard to SLN pathology and the distinction of nodal nevus cell rests/benign nevus cells and bland Spitz nevus cells in relation to melanoma metastasis. Immunohistochemistry

results can also be misleading and of little help in distinguishing the potential clinical behavior of nodal deposits of melanocytic cells.^{61–65} Urso et al. found that the histology of eight non-metastasizing atypical Spitz lesions exhibited the same characteristics as those of four lesions associated with nodal metastasis. All patients in these studies were alive and disease-free at a mean of 26.3 months.²⁹ Roaten et al. found that among pediatric and young adult melanoma patients 12–20 years of age, 40% of SLN biopsies studied were positive and without recurrences at a median follow-up of 35 months. Some of these patients may have had atypical Spitz nevi.⁵¹ Livestro et al. noted that 60% of patients (three of five) who had primary tumors classified as a MELTUMP had positive SLNs on biopsy.⁵³ Su et al. reported eight of 18 patients (44%) with Spitzoid melanocytic lesions had manifest SLN metastases. All underwent CLND with only one additional non-sentinel lymph node (13%) positive out of the group. These patients remained free of recurrent disease after 3–32 months of follow-up (mean = 12 months).²⁸

It has been argued that Spitz nevus cell aggregates in the lymph node may resemble a melanoma metastasis, making lymph node deposits in atypical Spitz tumors difficult to interpret.⁶⁶ This issue arises in regard to sentinel node biopsy for the diagnosis of Spitzoid melanoma.⁶⁶ CGH and fluorescence *in situ* hybridization (FISH) may illuminate these difficult cases and clarify risk of a lesion. As mentioned previously, CGH is a molecular cytogenetic screen for genetic changes and assesses changes in copy numbers of genes in a tumor compared to a reference sample.^{32, 67–70} In a report by Bastion et al, all benign nevi with aberrations were Spitz nevi and six of seven cases had an isolated gain of the short arm of chromosome 11 not observed in any of the melanomas.⁶⁷ Although not validated in large studies, this is the most concrete information we can get at assessing risk of local and regional metastasis in planning treatment for these. Currently, large scale studies are lacking, so selective use is warranted after multiple viewer consultations. Breslow's thickness should be ascribed to every Spitz/MELTUMP lesion for later analysis and current assessment. It is recommended that lesions with Spitzoid features should be completely excised (no specific margins). For those lesions with frank atypia where the subsequent biological behavior cannot be concluded, local surgical treatment as for a melanoma of equivalent depth is suggested. If possible, CGH/FISH may be considered in the treatment decision for these difficult cases.

In an effort to begin to obtain meaningful data for analysis of pediatric and young adult patients on a larger scale, a cooperative "International Pediatric Melanoma and Atypical Melanocytic Neoplasm" database has been developed by Drs. Averbook, Jukic, and Kirkwood with internet-based entry of de-identified data that can be updated. Accrual to the present time is 821 patients, with 451 melanomas and 370 atypical melanocytic neoplasms (including Spitz nevi and atypical Spitz nevi). Preliminary data show high rates of positive SLN biopsies, with 55 of 187 (29.4%) melanoma and 23 of 54 (43.5%) atypical melanocytic neoplasm patients with sentinel lymph node metastasis. At the time of this writing, the database is undergoing critical evaluation and statistical analysis. Mechanisms are being developed to capture tissue for molecular evaluation and considerations for CGH/FISH, and a pilot study is underway at the University of Pittsburgh focusing on adolescent and young adult melanoma patients (Panelli MC, Kirkwood JM, Tarhini AA. Personal communication, University of Pittsburgh; 2009). In lieu of prospective surgical adjuvant clinical trials in children, a large cooperative database may give us significant information to support patient management until prospective trials can be undertaken.

Adjuvant Medical Therapy of Melanomas of Pediatric and Young Adult Patients

Breslow's thickness and the presence of ulceration are the primary basis for systemic therapy, amplified by knowledge of the status of the regional lymph nodes for therapeutic decision-

making and patient counseling. Wright and colleagues have demonstrated that having a positive sentinel lymph node is associated with poor disease-free survival and OS for thin melanomas.⁷¹ While thin melanomas constitute over 80% of the melanomas recorded in the SEER Cancer Registry,¹ lesions between 0.76 and 1 mm have a lower yield of SLN positivity (approximately 6%).^{72,73} SNL biopsy is considered for melanomas thinner than 1 mm in selected high-risk patients. In a study of predictors of sentinel lymph node positivity that included an unusually high proportion of younger adults (of 429 participants, 76 were younger than 35), Sondak and colleagues found high-risk prognostic indicators included tumor ulceration, high mitotic rate, being male, and the presence of a vertical growth phase (as opposed to radial), as well as younger age.⁴¹

The use of adjuvant therapy for deep primary and regional node-positive melanoma continues to be controversial across the world, but this is generally pursued in the U.S. and should be weighed in light of the recent finding that nearly half of thin melanomas with a positive sentinel lymph node had recurrence within ten years and a ten-year melanoma-specific death rate of approximately 17%.⁷¹

Adjuvant Interferon for High-Risk Pediatric, Adolescent, and Young Adult Melanoma

In the United States, the only regimen approved by the federal Food and Drug Administration (FDA) is known as high-dose interferon alfa-2b (IFN α -2b). This regimen utilizes 20 million international units/meter squared (MIU/m²) of recombinant α -2b interferon in two phases—an intravenous induction treatment of five times weekly for four weeks, followed by a maintenance period of 10 MIU/m² subcutaneously three times weekly for 48 weeks.

Three major trials established IFN α -2b as the standard of therapy for adult melanoma in the U.S. In 1996, the Eastern Cooperative Group (ECOG) reported the pivotal trial E1684 introducing IFN α -2b as the first adjuvant therapy capable of significantly increasing recurrence-free survival (RFS) and overall survival (OS). E1684 randomized 287 adult patients with tumors greater than 4 mm or node-positive tumors to high-dose IFN α -2b or observation.⁷⁴ This study, like those that followed, age-stratified patients only as those younger or older than 50, making extrapolation of the findings to AYAs difficult. After nearly seven years of follow-up, IFN α -2b was demonstrated to prolong RFS and OS significantly, achieving an 11% estimated five-year RFS advantage (hazard ratio = 1.42).⁷⁵

This was followed by the Intergroup E1690 trial, which enrolled 642 patients with T4 primary disease or node-positive regional disease who were randomized to one of three arms: observation, high-dose IFN α -2b, or low-dose IFN α -2b of only 3 MIU/m² three times weekly. Those on high-dose IFN α -2b had improved median RFS but no difference in OS was observed in this trial. The study has been analyzed in great detail due to this difference from the earlier E1684 trial. One of the confounding factors in the trial was that patients were not required to have elective regional nodal dissections. Another confounding factor was that shortly after completion of enrollment, the data from E1684 became available and the FDA gave approval to high-dose IFN α -2b as a therapy for deep primary and node-positive patients—consequently nearly all patients who manifested nodal relapse after assignment to observation were able to obtain treatment with this regimen as a second-line treatment. Thirty-one percent of the observation patients went onto receive salvage therapy IFN α -2b, and the therapeutic impact of this treatment was noted to be substantial among those who were initially assigned to observation but later were treated at nodal relapse.⁷⁶

Finally, Intergroup E1694 was undertaken as a third study of high-dose IFN α -2b adjuvant therapy in which the GM2KLH/QS-21 vaccine (known as GMK) was tested in 880 patients.

This trial was closed after 16 months of follow-up when the data monitoring committee interim analysis showed significantly improved RFS and OS with high-dose IFN α -2b therapy compared to the GMK vaccine.⁷⁷ A pooled analysis of these studies with prolonged follow-up reported that RFS remained significantly improved with high-dose IFN α -2b therapy in two of the three trials, E1684 and E1690. Its finding after 12.6 years of follow-up that the benefits of E1684 were lower than initially reported may have been the result of increases in competing causes of death in the original study population, whose median age was 60 at the time of the pooled analysis.⁷⁵

The original study had high rates of side effects, with 67% of patients experiencing severe (grade 3) toxicity during the trial.⁷⁴ Concerns over the high rates of toxicity led to studies hoping to show an effect using low-dose IFN α instead, but those studies have largely shown either no or only short-term effects^{76, 78-80} and the U.K. AIM HIGH study was stopped before reaching its accrual goal due to lack of effect in early analyses.⁷⁹ Further, an ECOG study showed that the toxic effects of high-dose IFN α -2b can be offset by the clinical benefits.⁸¹

While the original finding of impact on RFS is now widely accepted, there remains much debate as to whether this translates into any long-term effect on OS. In 2003, noting the conflicting results of previous studies into IFN α , investigators of the European Organisation for Research and Treatment of Cancer (EORTC) published a meta-analysis of studies comparing high-dose IFN α and other intermediate-and low-dosage regimens to observation. They demonstrated that IFN α therapy significantly prolonged recurrence-free survival, with a trend toward a dose-response relationship in which higher doses had greater benefit. However, the resulting impact on overall survival including trials at a range of dosages remained unclear.⁸²

There remains much controversy over the use of interferon as adjuvant therapy for high-risk melanoma, but an updated individual patient data meta-analysis reported in 2008 demonstrated that there is a strong effect of IFN in aggregate across all trials upon relapse-free survival and also a significant but smaller effect upon overall survival.⁸³ In lieu of an alternative FDA-approved regimen for adults with melanoma, many efforts have been made to dissect and modify interferon therapy and to analyze the predictors of response that may allow refinement of this therapy for patients of all ages.

In the ECOG E1684 and the subsequent E1690 and E1694 Intergroup trials, it was anecdotally noted that interferon-assigned patients often developed thyroid hyperactivity and/or hypothyroidism, as well as vitiligo-like depigmentation. It remained, however, to carefully analyze the occurrence of serological evidence of the development of autoantibodies and other clinical manifestations of autoimmunity during therapy. Gogas and colleagues of the Hellenic Cooperative Oncology Group reported prospective observations within trial He13/A showing a striking difference in the therapeutic benefit achieved among individuals who did and did not develop manifestations of autoimmunity. This sub-study of the Hellenic trial of two modified derivative high-dose IFN α -2b regimens found autoantibodies and clinical manifestations of autoimmunity in 26% of patients; these patients had 50-fold improved RFS and OS.⁸⁴

Since 1999, it has also been known that melanoma is associated with constitutive induction of STAT3⁸⁵ as well as with immunologic tolerance in the T-helper cell type 2 immune responses.^{86, 87} Critchley-Thorne et al. have analyzed STAT1 phosphorylation signaling defects in the lymphocytes of patients with melanoma, demonstrating the capacity of high but not low concentrations of IFN to restore signaling in these T cells and other lymphocytes.⁸⁸ Thus, the analysis of autoimmunity induced in the host and of restoration of STAT1 phosphorylation defects in the blood lymphocytes of patients may provide insight into the patient population most sensitive to IFN therapy. The UPCI 00-008 trial examined the impact of neoadjuvant

therapy with high-dose IFN α -2b in terms of tumor tissue apoptotic, angiogenesis, and immunological effects.⁸⁹ Remarkably, this trial has shown a correlation of the influx of dendritic cells and T cells marked by CD11c and CD3, 4, and 8, respectively, and the antitumor effects of IFN manifest in regression of disease, which was observed among 11 of 20 subjects studied in this trial.⁸⁹ The therapy was associated with striking abrogation of the STAT3 induction found constitutively in melanoma. Thus, the neoadjuvant exploration of IFN has been fruitful—although none of this data can be directly extrapolated to the pediatric, adolescent, and young adult populations at this time.

It has been previously suggested that duration of treatment may also be important to outcome.⁹⁰ As such, it was hoped that pegylated IFN α -2b, by allowing prolonged therapy, would have a greater effect and provide improved balance of toxicity in relation to benefit. An EORTC study of pegylated IFN α -2b compared to observation noted a positive effect upon RFS, but there was no significant effect upon distant metastasis-free survival (DMFS) or overall survival, which were the original primary endpoints of the trial. The benefit of this regimen upon relapse-free survival among the subset of patients with microscopic nodal disease (N1 as termed by EORTC) was significant, and this subset of patients also exhibited benefit upon DMFS and OS. Toxicity with the planned more prolonged regimen remains an issue, as 45% of participants experienced a grade 3 or 4 adverse event, and 31% of patients had treatment requiring discontinuation because of toxicity. As with other studies, the published report does not allow extrapolation to the pediatric, adolescent, and young adult populations; this study included younger patients in the 18–49 age stratification.⁹¹ Also of note, the study was reported at a median duration of 3.8 years, far shorter than the 6.9 years at which E1684 results were first reported. With an impact that is confined to the microscopically involved stage IIIA (N1 per EORTC), this duration of follow-up is too short to be confident that the benefits will be enduring. Given the absence of any impact in patients with bulky nodal stage IIIB (N2 per EORTC), who comprised the majority of patients in the E1684 trial, and the comparison of pegylated interferon to observation rather than to high-dose IFN α -2b, it is difficult to know where the role of pegylated IFN will ultimately lie. The toxicities of this regimen do not appear to be noticeably different from non-pegylated IFN α , so the recommendation of five years of therapy for patients with stage IIIA disease (more than half of whom are cured by surgery alone) poses difficult issues for the oncologist. Without a direct comparison to high-dose IFN α , it is difficult to conclude whether pegylated IFN represents an improvement.

Several additional studies are also being carried out at the present time. The U.S. Intergroup trial E1697, joined by the National Cancer Institute of Canada (NCI-C), several sites in Australia, and available through the Cancer Trials Support Unit of the National Cancer Institute-Cancer Therapy Evaluation Program, is randomizing patients with intermediate risk (stage IIA, for which no therapy of benefit is available, and stage IIB-III A) to observation compared to IFN α -2b at the induction dosage derived from E1684 of 20 MIU/m² for five days per week for four weeks.⁹² The Hellenic Cooperative Oncology Group has investigated a modified induction regimen of 15 MIU/m² compared to this regimen followed by a modified maintenance regimen of 10 MIU/m² per day three times a week for one year, but it did not show any difference.⁸⁷ The German Dermatologic Cooperative Oncology Group (DeCOG) is conducting a clinical trial, MM-ADJ-5, testing induction therapy given without maintenance therapy on a repetitive four-monthly basis for three cycles. Patients receive the conventional E1684 high-dose interferon regimen versus induction therapy with 20 MIU/m² for five days per week for four weeks repeated every four months.⁹³

Despite continuing controversy, high-dose interferon remains the only adjuvant therapy approved by the U.S. FDA for resectable high-risk melanoma, with replicated, confirmed, and durable effects upon RFS, and with two trials that have shown benefit upon OS compared to observation and compared to the GMK vaccine.⁸² Interferon's efficacy can be improved using

specific subgroups, including a recent study showing that the group that may benefit the most is patients who have microscopic nodal involvement.⁹⁴ The tolerance of high-dose IFN among pediatric and young adult patients from 1.5–14 years of age has been noted to be improved, requiring fewer dose modifications than among adults.⁹⁵

Management of Metastatic Melanoma in Pediatric, Adolescent and Young Adults

For patients with stage IV metastatic melanoma, the prognosis remains poor, with a median survival time of less than one year and a five-year survival rate of less than 10%.³⁸ In the United States, there are currently only two FDA-approved treatments for the management of patients with metastatic melanoma—dacarbazine (DTIC) and interleukin-2 (IL-2).

DTIC shows some activity in metastatic melanoma and was reported to induce a 20–25% objective response.⁹⁶ The median duration of response is between four and six months with median survival less than nine months and six-year survival less than 2%.⁹⁶ The oral analog of dacarbazine, temozolomide (TMZ), has a theoretical advantage over DTIC in that it also crosses the blood-brain barrier and is spontaneously transformed to the active metabolite MTIC, where dacarbazine is metabolically transformed in the liver to the active agent and therefore does not reach the brain and third spaces in the body. Unfortunately, temozolomide is not approved for melanoma; further, a phase III trial of temozolomide reported nine years ago found median overall survival that was equivalent to that of dacarbazine, but not better.⁹⁷ A more recent and larger EORTC study of dacarbazine at standard 1000 mg/m² dosages compared to temozolomide at a dose-intensified alternate weekly regimen has shown no differences in OS or progression-free (PFS) between the two regimens, with response rates that are 10–15%.⁹⁸

In 1998, high-dose interleukin-2 was approved by the FDA for the treatment of metastatic melanoma based on the pooled findings of eight clinical trials with a combined 270 patients.⁹⁹ A later update showed an objective response rate of 16% and a complete response rate of 6%. The response was relatively durable with a median of 8.9 months, and best seen in patients who had soft tissue lymph node metastasis. The overall median survival was 12 months, but most significant was that at five years 11% of the patients were still alive.¹⁰⁰ While it is now accepted that with IL-2 therapy long-term durable responses are possible in a distinct subsets of patients, treatment with IL-2 is associated with significant toxicity requiring intensive care-level support and associated morbidity. As such, efforts to refine or lower the dose have been made, similar to such efforts with IFN α .

The next development was the combination of an immunological agent such as IL-2 or interferon in conjunction with chemotherapy, known as biochemotherapy. A phase III trial comparing sequential biochemotherapy with chemotherapy alone reported a response rate of 48% for the biochemotherapy arm versus 25% for standard chemotherapy. Despite the increased toxicity, the median OS improved from 9.2 to 11.9 months.¹⁰¹ The follow-up phase III Intergroup study, ECOG E3695, compared biochemotherapy to chemotherapy alone. A total of 395 patients were randomly assigned to either the biochemotherapy arm (N = 200) or the chemotherapy arm (N = 195). Biochemotherapy was associated with an increased response rate of 19.5% compared 13.8% and a longer RFS of 4.8 compared to 2.9 months. As with most melanoma treatment studies, there was no effect on OS.¹⁰²

New Strategies for Therapy of Melanoma

Currently, there is no established standard therapy available for metastatic melanoma, but novel therapeutic strategies continue to be investigated. A recent review of the past 35 years of North

American cooperative group phase II melanoma studies disclosed no regimens that appear to significantly improve OS or PFS—and sets new benchmarks for phase II studies to have a PFS rate of 15% at six months and an OS rate of 30% at 12 months. These appear to represent the natural history of melanoma. While there were small differences in outcome according to age that achieved statistical significance in relation to the PFS endpoint, these did not prove to be significant in relation to overall survival. The stratification of patients in this trial was into three categories with those below 46 years of age and those over 60 years of age demonstrating an adverse impact compared to the age group between 46 and 60. There was an interaction between age and performance status, with a substantially larger impact of performance status upon PFS. Performance status, the presence of visceral disease, the patient's gender, and the allowance of brain metastases in the particular trial were all significant predictors of OS.¹⁰³

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is a T cell surface receptor that acts to modulate the T cell responses by competing with CD28 for binding to the B7.1 and B7.2 receptors on antigen-presenting cells. Two antibodies, tremelimumab and ipilimumab, have recently completed their initial clinical trials. These studies demonstrate that clinical responses to tremelimumab and ipilimumab are associated with the development of autoimmune disease, with enterocolitis and dermatitis most commonly observed, suggesting increased activity of the immune system. For ipilimumab, a randomized trial demonstrating the use of a non-absorbed oral steroid used to treat the inflammatory colitis was not associated with affecting the efficacy of ipilimumab and did allow for immune-related adverse effects to be detected.¹⁰⁴ A phase I/II study of ipilimumab in 88 patients with stage III or IV disease given single doses up to 20 mg/kg, multiple doses up to 5 mg/kg, or multiple doses up to 10 mg/kg found an objective, durable response across all groups.¹⁰⁵ A dose-finding study for ipilimumab reported a dose-response relationship for doses 0.3, 3, and 10 mg/kg every three weeks or four doses followed by maintenance therapy every 12 weeks.¹⁰⁶ A clinical study of tremelimumab in previously treated melanoma patients with advanced refractory or relapsed disease showed an 8.3% objective response and a 22.8% clinical benefit rate, defined as an objective response plus stable disease at 70 days duration or more.¹⁰⁷ A phase III trial of tremelimumab on 655 patients with treatment-naïve stage IIIC or stage IV disease reported no significant benefit compared to standard chemotherapy with DTIC and TMZ, with an OS rate of 11.8% and 10.7%, respectively. Based on this lack of clinically significant benefit, the data safety monitoring committee recommended early termination of the trial.¹⁰⁸ One of the challenges with the modality of anti-CTLA-4 blocking antibodies has been that the onset of response can be variable in time, as late as several months into treatment, even after progressive disease and new manifestations of disease. The analysis of the phase III trial of tremelimumab is ongoing, and the reporting of the phase III trial of ipilimumab is still pending at this time—without data from either that pertain to pediatric, adolescent, or young adult patients.

Another recently developed and tested group of therapies is the group of targeted small molecules. The first of these is a group of agents that target the BRAF pathway. Sorafenib down-regulates BRAF and CRAF and has shown activity in patients with melanoma when combined with chemotherapy. The PRISM trial randomized 270 patients who had failed chemotherapy with DTIC or TMZ to paclitaxel and carboplatin with or without sorafenib and reported no benefit.¹⁰⁹ A large first-line cooperative group trial led by ECOG has assessed the role of sorafenib in combination with carboplatin and paclitaxel for patients who have not been exposed to cytotoxic chemotherapy.¹¹⁰ The more specifically targeted Raf-265 and broader multi-tyrosine kinase inhibitors (TKI, Novartis) are also now actively being explored in patients with advanced melanoma but no data that pertain to younger patients are available.¹¹¹

In summary, the treatment of melanoma in the pediatric, adolescent, and young adult populations requires new studies, and at present can only be extrapolated without validated outcome analyses from the adult population. The differing biology of melanoma and atypical

melanocytic neoplasms of the young would suggest that the outcomes for younger patients may be improved over those of adults, but the outcomes need to be studied in clinical trials of adequate size and maturity, with stratification for age in groupings that would allow us to draw meaningful conclusions regarding the behavior of melanoma in patients less than 15–39, 40–60, and those over 60. The study of the biology of melanoma in these age groups, particularly the immunological features of the disease and the host, will be rewarding. Currently, we simply know that melanoma in young patients is more likely to be found in regional lymph nodes, but less likely to recur in distant organs, with fatal outcome. The role of immunotherapies is likely to differ in the younger populations compared with those over 60, but has not been tested formally. The genetic lesions and progression markers of melanoma in the young are likely also to differ from those in melanoma of middle-aged and elderly populations—but this, too, has yet to be studied. The opportunity and challenge for specialists from a wide range of disciplines (dermatologists, surgical oncologists, and medical oncologists working with pathologists and molecular biologists, as well as tumor immunologists) will be to develop the scientific basis for improved therapy of melanoma in the young.

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TABLE 1

Comparison of Spitz nevus and melanoma (adapted from Elder & Murphy, 1991)

SPITZ NEVUS	MELANOMA
<i>< 6 mm</i>	<i>> 6 mm</i>
<i>Symmetrical</i>	<i>Asymmetrical</i>
<i>Epidermal changes</i>	<i>No epidermal reaction</i>
<i>Discontinuous junctional growth</i>	<i>Continuous junctional growth</i>
<i>Some pagetoid acceptable</i>	<i>Pagetoid obvious</i>
<i>Mitoses - low or rare</i>	<i>Mitoses rarely absent</i>
<i>Uniformly atypical - maturation seen</i>	<i>Atypical - no maturation</i>
<i>Small dermal nests</i>	<i>Large dermal nests</i>