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Thoracic metastasectomy for adoptive immunotherapy of melanoma: A single-institution experience

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Objectives: Although refractory to chemotherapy, metastatic melanoma may respond to adoptive immunotherapy. As novel treatments evolve, surgeons may be asked to perform metastasectomy not only for palliation or potential cure but also for isolation of tumor-infiltrating lymphocytes. This study was undertaken to examine outcomes of patients with melanoma undergoing thoracic metastasectomy in preparation for investigational immunotherapy.

Methods: A retrospective review identified 107 consecutive patients who underwent 116 thoracic metastasectomy procedures from April 1998 to July 2009. Indications for surgical intervention included procurement of tumor-infiltrating lymphocytes, rendering of patients to no evaluable disease status, palliation, and diagnosis. Response Evaluation Criteria in Solid Tumors criteria were used to assess tumor response.

Results: Thoracotomy, lobectomy, and video-assisted thoracoscopic surgery with nonanatomic resection were the most common procedures. Major complications included 1 death and 1 coagulopathy-induced hemothorax. Seventeen patients were rendered to no evaluable disease status. Virtually all patients with residual disease had tumor specimens cultured for tumor-infiltrating lymphocytes; approximately 70% of tumor-infiltrating lymphocyte cultures exhibited antitumor reactivity. Of the 91 patients with residual or recurrent disease, 24 (26%) underwent adoptive cell transfer of tumor-infiltrating lymphocytes, of whom 7 exhibited objective responses (29% response rate and 8% based on intent to treat). Rapid disease progression precluded tumor-infiltrating lymphocyte therapy in most cases. Actuarial 1- and 5-year survival rates for patients rendered to no evaluable disease status or receiving or not receiving tumor-infiltrating lymphocytes were 93% and 76%, 64% and 33%, and 43% and 0%, respectively.

Conclusions: Relatively few patients currently having thoracic metastasectomy undergo adoptive cell transfer. Continued refinement of tumor-infiltrating lymphocyte expansion protocols and improved patient selection might increase the number of patients with melanoma benefiting from these interventions. (J Thorac Cardiovasc Surg 2010;140:1276-82)

Malignant melanoma is a highly lethal disease, the incidence of which continues to increase at an alarming rate.[1] In 2008, the estimated incidence of melanoma was 62,480; approximately 8420 deaths were attributable to this disease.[2] Patients with metastatic melanoma have a median survival of 6 to 8 months and a 5-year survival approximating 6%.[3,4]

The standard treatment for patients with metastatic disease is systemic interleukin 2 (IL-2) or chemotherapy.[5-7] Response rates associated with these regimens are relatively low, and complete responses are rare.

Translational research efforts by several groups throughout the world, including the Surgery Branch, National Cancer Institute, have focused on the development of protocols using adoptive cell transfer (ACT) of autologous tumor-infiltrating lymphocytes (TIL) to augment immune-mediated eradication of metastatic melanoma. TIL therapy requires the resection of metastatic lesions to harvest tumor-reactive T lymphocytes, which are selectively expanded ex vivo and subsequently infused with high-dose IL-2 into autologous lymphodepleted patients. Recent data indicate clinical response rates exceeding 50% for patients with melanoma undergoing ACT with autologous TIL.[8]

Because of the need for expeditious ex vivo expansion of TIL cultures, an increasing number of patients with melanoma lacking bulky subcutaneous or lymph node metastases have been referred for more extensive operations to harvest

> **Abbreviations and Acronyms**
> ACT = adoptive cell transfer
> IL-2 = interleukin 2
> NED = no evaluable disease
> NMA = nonmyeloablation
> TBI = total-body irradiation
> TIL = tumor-infiltrating lymphocyte

lesions sufficient for TIL production. However, as more invasive procedures are performed to render patients with limited overall median survivals eligible for ACT protocols, the potential risks and morbidities of metastasectomy must be carefully assessed relative to the probabilities that these patients will receive and respond to TIL therapy. The present study was undertaken to evaluate outcomes and potential benefits of thoracic metastasectomy for adoptive immunotherapy of melanoma.

MATERIALS AND METHODS
Patients

A retrospective review of a prospectively collected database identified patients who underwent thoracic metastasectomy for melanoma in the context of immunotherapy from April 1998 to July 2009. All patients signed institutional review board–approved consent forms for tissue procurement and participation in subsequent immunotherapy protocols, if indicated. Patients with metastatic melanoma considered for experimental immunotherapy were 18 years of age or older and negative for HIV and hepatitis B and C, with a good performance status (Eastern Cooperative Oncology Group class ≤2) and life expectancy greater than 3 months. Patients were enrolled in sequential phase II protocols, the first 3 of which differed in terms of lymphodepletion regimens, whereas the fourth differed in terms of laboratory preparation/analysis of TIL. All surgical procedures were performed by 3 surgeons (DSS, DMN, and KFK) in the Thoracic Oncology Section of the Surgery Branch, National Cancer Institute.

Surgical Intervention and Continuing Care

Complete staging was performed with history and physical examination, laboratory assessment, and computed tomographic examination of the chest, abdomen, and pelvis. Additional studies were performed based on individual patient assessments. Patients did not necessarily have pathologic confirmation of melanoma in the thorax before metastasectomy. Postoperative pathology was confirmed in all patients. A patient's suitability for thoracic resection was predicated on his or her ability to tolerate an operation, pace of disease progression, absence of central nervous system or symptomatic intra-abdominal disease, and the likelihood of subsequently participating in an immunotherapy protocol. Ability to achieve a complete resection was not a criterion for surgical intervention; indeed, the most common indication was isolation of TIL in patients with widely metastatic disease. Decisions to operate were made on a case-by-case basis after thorough review during a weekly multidisciplinary conference. The decision to resect all pulmonary disease or simply harvest lesions sufficient for generating/expanding TIL was determined preoperatively based on overall extent of disease. In addition, central lesions associated with postobstructive atelectasis or pneumonia were targeted for resection to simultaneously harvest TIL and prevent potentially fatal septic complications during ACT. In essence, the goal in patients with surgically incurable disease was to harvest a minimum of 3 cm^3 of viable tumor and resect obstructing lesions with minimal

morbidity to facilitate movement of these subjects to potentially curative immunotherapy protocols. Patients rendered to no evaluable disease (NED) status were evaluated every 3 months for the first year, every 6 months for the next 2 years, and annually thereafter.

TIL Production and Administration

After resection, all tumors were processed in the Cell Production Facility of the Surgery Branch for isolation/expansion of TIL using previously described techniques.[9] Before July 2007, the activity and specificity of expanded TIL were evaluated by means of cytokine release assays with a panel of tumor targets, including allogeneic melanoma cell lines, fresh autologous tumor cells (or autologous tumor cell lines when available), and peptide-pulsed transporter associated with antigen processing–deficient T2 cells. During that period, interferon γ secretion by TIL appeared to correlate with in vitro tumor cytotoxicity and in vivo efficacy. From July 2007 through July 2009, cultures that successfully yielded TIL were administered without in vitro reactivity analysis given advancements in cell processing and administration, and concerns that in vitro assays lacked sufficient sensitivity and specificity to accurately reflect in vivo efficacy.[10]

TIL that met the criteria for infusion underwent rapid expansion with OKT3 (anti-CD3) antibody (Ortho Biotech, Bridgewater, NJ), recombinant IL-2 (Chiron Corp, Emeryville, Calif), and irradiated peripheral blood mononuclear cells. After 14 days, these cells were harvested, and on average, 6×10^{10} TIL were administered to autologous hosts by means of a 30-minute intravenous infusion after nonmyeloablation (NMA) with cyclophosphamide (60 mg · kg^{-1} · d^{-1} × 2 days) and fludarabine (25 mg · m^{-2} · d^{-1} × 5 days); several patients also received total-body irradiation (TBI) at a dose of 200 or 1200 cGy. After TIL infusion, most patients received intravenous high-dose IL-2 up to 15 doses or until exhibiting dose-limiting toxicity, which resolved in all patients within 7 days. Patients with neutropenic fevers received antibiotics, which continued until full return of immunologic function (typically 7 days). Under these regimens, the minimum time from operation to TIL therapy was 6 to 8 weeks.

Assessment of Response

After cell transfer, patients were assessed radiographically for tumor response by using Response Evaluation Criteria in Solid Tumors every month for 6 months, every 3 months for a year, and every 6 months thereafter.[11] Complete responders had no radiographic evidence of residual tumor after therapy. Partial responders were patients exhibiting a 30% or greater decrease in the sum of the longest diameters of their target lesions. Patients were deemed to have progressive disease if they exhibited a 20% or greater increase in the sum of the longest diameters of their target lesions or had new lesions. All radiographic images were reviewed independently by an attending surgeon and a staff radiologist. Imaging studies of patients exhibiting an objective response were confirmed by at least 1 additional attending physician.

Statistical Analysis

Overall survival was calculated from the date of resection until the date of last encounter or death. The date of first resection was used in patients who underwent 2 operations. The probabilities of survival were calculated by using Kaplan–Meier methods.

RESULTS

From April 1998 until July 2009, 107 patients with metastatic melanoma underwent 116 thoracic metastasectomy procedures, including 9 patients who underwent 2 separate procedures (Table 1). Ninety-six (90%) patients received systemic treatment for metastatic melanoma before metastasectomy. More than 50% of patients received high-dose IL-2. Approximately 60% of patients received 2 different

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TABLE 1. Clinical characteristics of 107 patients who underwent thoracic metastasectomy for metastatic melanoma

Characteristic	Value
Feature	
No. of patients	107
Age, median (range) at operation (y)	47 (18–67)
Sex, M/F	61/46
Tobacco use	
Yes	29 (27%)
No	78 (73%)
Prior treatment (per patient)	
None	11 (10%)
Interferon alpha 2b	37 (35%)
Interleukin 2	65 (61%)
Adoptive cell transfer	15 (14%)
Chemotherapy	26 (24%)
Biochemotherapy*	15 (14%)
Vaccine	41 (38%)
Anti–CTLA-4 antibody	13 (12%)
Indication for metastasectomy (per case)	
TIL	79 (68%)
NED	9 (8%)
Diagnosis	1 (1%)
Palliation of symptoms	2 (2%)
Progressive disease	4 (3%)
TIL/palliation	8 (7%)
TIL/NED	12 (10%)
TIL/diagnosis	1 (1%)
Surgical approach (per case)	
Thoracotomy	69 (59%)
VATS	43 (37%)
Sternotomy	3 (3%)
Other	1 (1%)
Procedure (per case)	
Lobectomy	23 (20%)
Nonanatomic (wedge)	66 (57%)
Segmentectomy	5 (4%)
Lingulectomy	1 (1%)
Pneumonectomy	2 (2%)
Chest wall resection	6 (5%)
Other	13 (11%)
Status after metastasectomy	
Residual disease	90 (84%)
NED	17 (16%)
No. of metastases resected in patients rendered to NED status†	
1	13
2	4
≥3	2

CTLA-4, Cytotoxic T lymphocyte–associated antigen 4; *TIL*, tumor-infiltrating lymphocytes; *NED*, no evaluable disease; *VATS*, video-assisted thoracoscopic surgery. *Biochemotherapy = chemotherapy combined with interleukin 2 or interferon α. †Includes 2 patients rendered NED twice (n = 19).

types of treatment, and 30% received 3 or more regimens, including chemotherapy, immunotherapy, vaccines, or investigational agents in various combinations. Fifteen patients were treated with ACT of autologous TIL or genet-ically engineered peripheral blood lymphocytes before metastasectomy; 3 of these patients were retreated with TIL after thoracic metastasectomy. There was 1 postoperative death caused by pulmonary embolism and 1 coagulopathy-induced hemothorax treated with recombinant activated Factor VII and evacuation of clot in a patient undergoing pneumonectomy for postobstructive pneumonia and hemodynamically significant mediastinal compression. Morbidities, such as atrial arrhythmia, persistent air leak, or pneumonia, were exceedingly rare (low single digits), possibly due to lower median age, less tobacco exposure, absence of significant cardiopulmonary comorbidities, and improved overall performance status of the immunotherapy protocol candidates relative to patients typically undergoing lung cancer resections.[12,13]

The most common single indication for surgical intervention was procurement of TIL (79/116 [68%]). Frequently, the indications for surgical intervention overlapped. Additional indications, included resection to NED (21/116 [18%]), diagnosis (2/116 [2%]), solitary site of progressive disease after systemic therapy (4/116 [3%]), and palliation of hemoptysis, bronchial obstruction, hemothorax, and/or pleural effusion (10/116 [9%]). Eight of the 10 patients requiring surgical intervention for palliation had TIL cultures established from the resection specimens.

One hundred one tumor specimens from 116 procedures were cultured for TIL. Of the 15 tumors not cultured for TIL, 8 patients were resected to NED, and 2 had rapid progression of disease, death, or both; 5 tumors were not processed for unknown reasons (possibly because of the small size of the lesions). Ninety-three (92%) of 101 TIL cultures were considered growth positive (Table 2). Sixty-nine growth-positive cultures were tested for activity, 47 (68%) of which were reactive based on laboratory criteria. Twenty-four cases of growth-positive TIL were not tested because the respective patients had stable disease, were rendered to NED status, or were excluded because of significant disease progression or treatment on an alternate immunotherapy protocol. For 7 patients treated after July 2007, growth-positive TIL cultures were not tested for in vitro tumor reactivity because of the aforementioned modifications of TIL expansion protocols. Twenty-four (26%) patients with residual disease, including 1 patient who was rendered to NED status and subsequently had recurrent disease, were treated on various TIL protocols (Figure 1).

The reasons patients did not receive TIL are listed in Table 2. Patients with tumor cultures that did not grow TIL or growth-positive cultures that did not meet the criteria for reactivity before July 2007 were unable to be treated. Despite having reactive TIL, some patients did not undergo ACT because of rapid, uncontrollable disease progression (typically involving the spine or central nervous system with symptoms or potential risk of bleeding while thrombocytopenic, gastrointestinal tract with bleeding or obstruction, or new
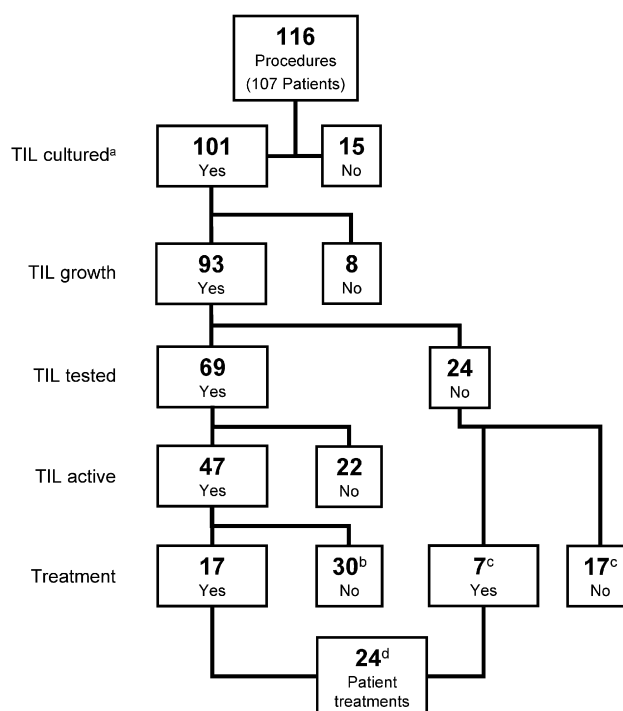
TABLE 2. Results of TIL growth, testing, and therapy

Characteristic	Value
No. of tumor specimens obtained	116
Cultured	101
Not cultured	15
TIL growth (per specimen cultured)	
Positive	93 (92%)
Negative	8 (8%)
TIL activity tested	69
Reactive	47 (68%)
Nonreactive	22 (32%)
TIL activity not tested	24
Treatments after metastasectomy (per patient)	
TIL	24
No TIL	83
Reasons for no TIL treatment*	
Progressive disease	25 (27%)
TILs not reactive in vitro	20 (22%)
NED	18 (20%)
Alternate protocol assignment	8 (9%)
TILs did not grow	6 (7%)
Protocol exclusion	4 (4%)
Stable disease	3 (3%)
Death	3 (3%)
Unknown	5 (5%)
Objective response to TILs	
Complete response	2
Partial response	5
No response	15
Not evaluable for response	2

TIL, Tumor-infiltrating lymphocyte; *NED*, no evaluable disease. *There were 92 instances in which TIL therapy was considered, including 9 patients who were resected twice.

FIGURE 1. Flow diagram of patients undergoing thoracic metastasectomy for melanoma immunotherapy. Patients are classified according to status of tumor-infiltrating lymphocyte *(TIL)* culture, TIL growth, TIL activity in vitro, and treatment with TIL or not. [a]TIL cultures per procedure. [b]Includes resection, and no treatment twice for 1 patient. [c]One patient included in each group because of first resection and treatment followed by recurrence, and second resection and no subsequent treatment. [d]Representative of 24 individual patient's treatments.

pulmonary lesions causing bleeding or postobstructive infections, all of which were exclusion criteria for TIL protocols), death, alternate protocol assignment, or NED status. Before July 2007, the average time from operation to treatment with TIL was 6 to 8 weeks. During TIL expansion, patients did not receive systemic treatment for melanoma, and many had rapidly progressive disease, as noted above, or exhibited a significant decrease in performance status resulting in protocol ineligibility or death. The advent of short-term TIL culture techniques and the elimination of in vitro testing before treatment shortened the interval from operation to TIL therapy by approximately 2 weeks. Of the 26 patients who underwent thoracic metastasectomy after July 2007, the proportion of patients receiving "young" TIL without assessment of in vitro tumor reactivity (8/26 [31%]) was somewhat higher than that of the preceding cohort receiving "conventional" TILs (16/82 [20%]). One patient underwent surgical intervention in both cohorts.

Seventeen patients were rendered to NED status at the time of surgical intervention. The number of metastatic lesions removed was 1 in 13 cases, 2 in 4 cases, and 3 or more in 2 cases. Two patients had a recurrence more than

1 year after their operations, and underwent repeat thoracic metastasectomy to render them free of disease again. One patient who was rendered to NED status after metastasectomy had recurrent disease 5 months later and was treated with TIL. Because the intent of that procedure was not only to remove all gross tumor but also to generate TIL, this patient is included in the TIL group for survival analysis. Although 10 of the remaining 16 patients rendered to NED status at the time of metastasectomy had tumor specimens cultured for TIL, this group was never treated with TIL and is considered separately in analysis of survival.

Of the 24 patients receiving TIL therapy, 2 had complete responses and 5 had partial responses, for an overall treatment response rate of 29%. Based on preoperative intent-to-treat, patients with residual or recurrent disease, the overall response rate was 8% (7/91). Sixteen patients had no response to treatment. Six (35%) of 17 patients treated with conventional TIL compared with 1 (14%) of 7 receiving young TIL exhibited objective responses. Two patients were not evaluable, one because of treatment-related mortality and the other because of treatment proximate to this analysis. Aside from the single treatment-related mortality, toxicities associated with ACT were reversible and
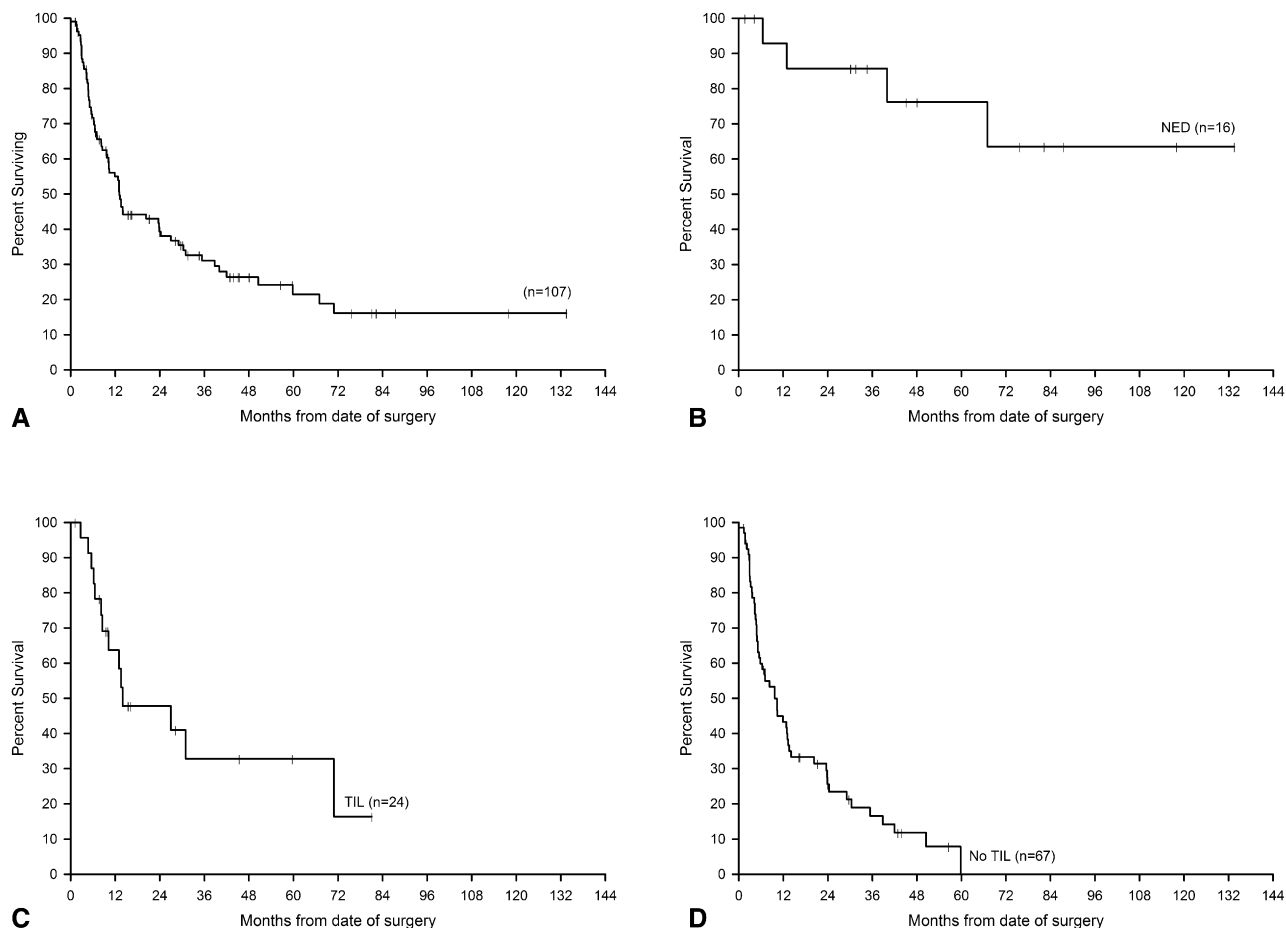
FIGURE 2. A, Overall survival of 107 patients undergoing thoracic metastasectomy for melanoma immunotherapy. The median survival was 13.2 months, with a 5-year survival rate of 22%. B, Survival of patients rendered to no evaluable disease *(NED)* status after surgical intervention. The median survival for these patients has not been reached. C, Survival of patients with residual disease after metastasectomy who received tumor-infiltrating lymphocyte *(TIL)* therapy. Median survival of these patients was 14 months. D, Survival of patients with residual disease after metastasectomy who did not receive TIL therapy. Median survival of these patients was 10 months.

consistent with recently published Surgery Branch data.[8] The median survival for all patients in this study was 13.2 months (Figure 2, *A*). As of January 15, 2010, the median survivals for patients who received TIL and those who did not receive TIL were 14 and 10 months, respectively. The median survival for patients undergoing potentially curative resections has not been reached. Actuarial 1- and 5-year survival rates for patients rendered to NED status, receiving TIL, or not receiving TIL, were 93% and 76%, 64% and 33%, and 43% and 0%, respectively (Figure 2, *B–D*, respectively).

DISCUSSION

Whereas approved chemotherapeutic regimens as well as targeted molecular agents for metastatic melanoma afford patients limited chance for long-term survival,[6,14] ongoing research in cancer immunology offers hope for patients with this disease. Presently, approximately 15% of patients treated with high-dose IL-2 exhibit objective tumor regressions, half of which are durable complete responses.[15] Similar response rates have been observed in patients with melanoma after monoclonal antibody blockade of cytotoxic T lymphocyte–associated antigen 4.[16,17]

The response of metastatic melanoma to immunotherapy provides the impetus for refinement of cell-based regimens for patients with this disease.[18] Dudley and colleagues[8] reported results pertaining to 93 patients with melanoma treated with TILs after several lymphodepletion regimens; response rates were 48%, 52%, and 72% for NMA, NMA plus 200 cGy TBI, and NMA plus 1200 cGy TBI, respectively. Because tumor reactivity was a prerequisite for treatment on these protocols, each patient's TIL culture underwent an individualized screening assay. Tumor progression during the extended time for TIL production or a negative tumor reactivity screen result rendered approximately 73% of patients who underwent tissue procurement ineligible for ACT.

Because of improved responses to immunotherapy in sequential clinical trials within the Surgery Branch, efforts to

optimize TIL production have evolved to include surgical procedures once considered unconscionable for patients with disseminated melanoma. To the best of our knowledge, this article is the first reported experience pertaining to patients with melanoma undergoing thoracic metastasectomy solely in the context of experimental immunotherapy protocols. Unlike other reported series,[19-21] in our study metastasectomy was performed in most patients not to render them to NED status but to facilitate their eligibility for ACT. Despite these highly focused efforts, relatively few patients with residual disease ultimately underwent ACT, primarily because of lack of TIL reactivity or rapidly progressive disease. This is unfortunate because patients who received TIL infusions after thoracic metastasectomy had a 5-year actuarial survival of 33%, whereas none of those who did not undergo ACT survived 5 years. The fact that response rates after TIL therapy in our series are lower than those reported by Dudley and colleagues[8] may be attributable to the relatively low number of patients treated, as well as suboptimal TIL production and host preparative regimens (only approximately 25% of patients received TBI), highlighting the clinical relevance of the evolution of TIL efforts in the Surgery Branch.

Although thoracic metastasectomy was associated with low mortality and minimal morbidity, the fact that relatively few patients in our study ultimately received TIL therapy raises concerns regarding the ethics of subjecting patients with advanced malignancies and limited life expectancies to invasive procedures in the context of highly experimental treatment protocols, particularly in an era of dwindling health care resources.[22] On the other hand, our experience demonstrates an evolving role of thoracic surgery in facilitating development of innovative systemic cancer regimens. Furthermore, our data highlight the fact that patients considered for protocols contingent on procured tumor specimens must be fully appraised of the potential risks and morbidities of their respective surgical procedures, as well as the likelihood that they will receive and ultimately respond to investigational therapy, to make informed decisions regarding their care.[23]

Results of this analysis are consistent with data pertaining to a recent unpublished evaluation of metastasectomy and TIL therapy within the Surgery Branch. Between 2002 and 2007, 402 patients underwent 541 procedures, yielding viable and reactive TIL in 376 (94%) and 269 (67%) patients, respectively; 107 (27%) patients underwent ACT. In light of the collective experience, considerable efforts have been underway within the Surgery Branch to optimize TIL production. A recent series of experiments revealed that minimally cultured TIL exhibited optimal characteristics for ACT, including tumor reactivity,[10] which obviated the requirement for in vitro screening that previously disqualified patients from receiving therapy. Translation of these observations to a phase II clinical trial for the treatment of patients with melanoma using minimally cultured TIL resulted in higher patient recruitment rates, shorter times between resection and treatment, and response rates comparable with those seen with conventional TIL (Dudley and colleagues, submitted for publication). These data suggest that an additional 20 patients or more in our study who did not undergo ACT because of a lack of TIL reactivity or rapid disease progression might have been candidates for potentially beneficial TIL therapy. Ongoing efforts are focused on identification of prognostic and predictive markers to improve patient selection and further optimization of TIL protocols to enhance overall response rates, thereby minimizing the number of futile metastasectomy procedures.

Approximately 25% of patients with melanoma have pulmonary metastases, resection of which was proposed as potentially beneficial before the advent of effective systemic therapy.[24] More recent studies have confirmed the benefit of complete resection in patients with melanoma with oligometastatic disease involving the lungs; in the absence of effective systemic therapy, the role of metastasectomy remains limited for the majority of patients with disseminated melanoma.[19,21,25] Our data are consistent with these observations. Although the goal of our study was to review the potential utility of thoracic metastasectomy as a means to render patients eligible for adoptive immunotherapy rather than definitive treatment for metastatic melanoma, it is noteworthy that 17 patients in our study underwent resection of all evaluable disease, with 12 alive today (Figure 1). The 5-year actuarial survival (76%) of this group exceeds that reported for patients undergoing complete resection in other series.[19,21,25] Whereas these findings are certainly attributable in part to patient selection, it is intriguing that 15 of these patients had received some form of immunotherapy (IL-2, vaccine, or interferon) before undergoing resection. One patient who was rendered to NED status subsequently had recurrent disease that was treated with TIL. This patient's experience highlights the potential value of cryopreserving melanoma lesions for future immunotherapy protocols given the high likelihood of disease recurrence.

Potential limitations of this study include the retrospective manner of data analysis, as well as selection bias inherently resulting from the fact that patients were not prospectively randomized to treatment regimens; these issues limit firm conclusions regarding survival rates. Inevitably, patients with slowly growing metastases and good performance status exhibited a more favorable tumor biology, which enabled them to be referred for thoracic metastasectomy and undergo TIL therapy. In contrast, patients unable to receive TIL therapy had more aggressive tumors that might have been refractory to any interventions.

Despite the fact that patients referred for surgical intervention were highly selected, this experience is noteworthy for demonstrating the potential benefits of TIL therapy in patients

with melanoma with otherwise dismal prognoses. Whereas thoracic metastasectomy cannot be routinely advocated for patients expected to have residual disease, these operations might yield TIL that can mediate durable tumor regressions. Given the encouraging results of TIL therapy,[8] patients with melanoma with thoracic metastases should be referred to centers of excellence in cancer immunotherapy to determine their eligibility for potentially curative ACT protocols.

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