Published in final edited form as:

Ann Surg Oncol. 2010 January ; 17(1): 163–170. doi:10.1245/s10434-009-0677-0.

Liver Resection for Metastatic Melanoma with Postoperative Tumor-Infiltrating Lymphocyte Therapy

R. Taylor Ripley, MD¹, Jeremy L. Davis, MD¹, Jacob A. Klapper, MD¹, Aarti Mathur, MD¹, Udai Kammula, MD¹, Richard E. Royal, MD¹, James C. Yang, MD¹, Richard M. Sherry, MD¹, Marybeth S. Hughes, MD¹, Steven K. Libutti, MD¹, Donald E. White, MS¹, Seth M. Steinberg, PhD², Mark E. Dudley, PhD¹, Steven A. Rosenberg, MD, PhD¹, and Itzhak Avital, MD¹

¹Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD;

²Biostatistics and Data Management Section, Office of the Clinical Director, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Rockville, MD

Abstract

Background.—Patients with metastatic melanoma to the liver (MML) have a median survival of 4 to 6 months. This study evaluated patients who underwent liver resection with intent to receive postoperative tumor-infiltrating lymphocyte (TIL) therapy.

Methods.—Retrospective analysis of a prospective database identified patients with MML who underwent liver resection from 1980 to 2008.

Results.—A total of 539 patients had MML, and 39% (204 of 539) had tumor collected for TIL. A total of 17% (35 of 204) underwent liver resection for TIL. The 3-year overall survival was 53%. Lack of extrahepatic disease ($P = .026$), negative margin ($P = .056$), and single hepatic metastasis ($P = .04$) predicted survival after univariate analysis. Only lack of extrahepatic disease remained a significant predictor of survival after multivariate analysis ($P = .043$). A total of 31% (11 of 35) underwent complete resection without TIL, and 69% (24 of 35) underwent resection with synchronous intrahepatic and extrahepatic disease with intent to receive TIL. For 9 of 11 patients (2 of 11 excluded for gene therapy), 3-year survival was 80%. A total of 4 (44%) of 9 experienced recurrence, with a median disease-free survival of 1.2 years. For 24 patients (69%) with residual disease, 3-year survival was 51% (2 of 24 excluded for gene therapy). A total of 63% (15 of 24) received postoperative TIL (3-year survival 65%), and 29% (7 of 24) did not. A total of 40% (6 of 15) had disease that partially responded to TIL; the disease of 67% (4 of 6) had not progressed at median follow-up of 55 months (range, 42–197? months). The seven patients who did not receive TIL had a median survival of 4.6 months.

Conclusions.—Resection of MML with TIL should be considered because it can result in prolonged survival in a highly selected group of patients.

The estimated incidence of cutaneous melanoma in 2008 was 62,480 cases, and the number of deaths was estimated to be 8,420.^{1–3} Metastatic melanoma (MML) portends a dismal prognosis, with median survival of 6 to 7.5 months and a 5-year survival of 6%.⁴ Approximately 15% to 30% of patients with MML have liver disease, but autopsy reports

suggest that the actual incidence may be higher (54% to 77%).⁵ The median survival of patients with metastatic disease in the liver is 4.4 months.

The standard treatment for patients with MML is systemic therapy with either interleukin-2 (IL-2) or chemotherapy.^{6–9} Surgical resection is usually not recommended. However, several studies reported that a highly selected group of patients may benefit from liver resection.^{10–22} Despite these reports, most patients are not evaluated for resection.

Immunotherapy has emerged as a promising treatment resulting in durable complete remission in certain patients with MML.^{23,24} The adoptive transfer of autologous tumor-infiltrating lymphocytes (TIL) supported with IL-2 infusion after lymphodepleting chemotherapy has mediated objective clinical response rates in 52 (56%) of 93 patients.^{25–27} To produce TIL, a tumor must be resected and the infiltrating lymphocytes cultured and grown ex vivo. The tumors must be $\geq 3 \text{ cm}^3$ to obtain an adequate TIL culture. Ideal resections for generating TIL involve low-morbidity procedures. Occasionally, the only tumors available for collection are hepatic metastases.

The objective of this study was to review the overall experience with liver resections for MML in the Surgery Branch, National Cancer Institute, National Institutes of Health. We specifically evaluated patients who were resected to no evidence of disease (NED) and patients who underwent hepatic resection with residual disease and the intent to receive TIL.

PATIENTS AND METHODS

Data Collection and Clinical Assessment

A retrospective review of a prospectively collected database identified patients who underwent hepatic resection and a diagnosis of melanoma at the National Cancer Institute (Bethesda, MD) for the years 1980 until 2008. Inclusion criteria included pathologically confirmed MML from a resected liver lesion. Exclusion criteria involved radiofrequency ablation, embolization, needle biopsy, or an open biopsy during isolated hepatic perfusion for ocular melanoma. All patients signed an institutional review board–approved consent for tissue procurement and for participation in clinical studies if the patient proceeded to further therapy.

Patients with MML who were considered to be treated by TIL were aged ≥ 18 years, negative for hepatitis B and C and for human immunodeficiency virus, had good performance status (Eastern Cooperative Oncology Group score ≤ 2), and had a life expectancy of >3 months. The disease of all patients was refractory to systemic therapy.

TIL Therapy

Patients were treated with cyclophosphamide (60 mg/kg) for 2 days followed by fludarabine (25 mg/m²) for 5 days as a nonmyeloablative preparative regimen. Some patients also received 2 Gy total-body irradiation with autologous stem-cell transplantation. The day after chemotherapy, approximately 5×10^{10} TIL cells were infused and supported with 720,000 IU/kg of IL-2 every 8 hours to tolerance or to a maximum of 15 doses.

Surgery and Continuing Care

Complete staging was performed with history and physical examination, laboratory assessment, computed tomography of the chest, abdomen, and pelvis, and magnetic resonance imaging of the brain and liver for all patients. Additional studies were performed on the basis of individual patient assessment. Patients did not necessarily have confirmation of melanoma in the liver by pathology before the operation. Postoperative pathology was confirmed in all patients.

Suitability for hepatic resection was based on the patients' ability to tolerate an operation, as well as the likelihood of proceeding to an immunotherapy protocol. Ability to achieve R0 resection was not a criteria given that the intent to resect a lesion was the generation of TIL. Decisions to operate were made on a case-by-case basis during presentation at the Surgery Branch preoperative conference. The decision to resect all liver disease versus enough liver disease to generate TIL was based on pre-operative and intraoperative findings with assistance of intraoperative ultrasound.

Patients with residual disease were assessed for enrollment onto immunotherapy protocols as soon as they had recovered from the operation. Patients resected to NED were evaluated every 3 months for the first year, then every 6 months for the next 2 years, then annually. Continuing care and the administration of chemotherapy was facilitated by the patient's local oncologist.

Evaluation of Responders

World Health Organization criteria or Response Evaluation Criteria in Solid Tumors were used to assess responses. All radiographic images were reviewed by an attending surgeon and an independent radiologist. Films for patients who had an objective response were reviewed by at least one additional attending physician.

Statistical Analysis

Overall survival (OS) was calculated from the date of hepatic resection until the date of the last encounter or date of death, as appropriate. For the patients resected to NED, disease-free survival was calculated as the time from the hepatic resection until the first recurrence, or the last follow-up without a recurrence, as appropriate. For patients with residual disease after the operation, progression-free survival (PFS) was calculated from the date of liver resection until progression of disease at any site or the last follow-up without progression, as appropriate. The probabilities of survival, disease-free survival, or PFS were calculated by the Kaplan-Meier method; the statistical significance of the difference between pairs of Kaplan-Meier curves was determined by the log rank test for cases in which the distinguishing characteristic of the curve was known at the date of resection.

Clinicopathologic features including demographics, initial American Joint Committee on Cancer stage, disease-free interval (DFI) 1 and 2, recurrence pattern, preoperative systemic therapy, and operative findings were evaluated for their association with outcome by univariate methods described above, as well as a Cox proportional hazard model to assess if factors may jointly influence the outcome. Preoperative systemic therapies analyzed

included IL-2, chemotherapy, adoptive cell transfer, and vaccination. This analysis was performed for the entire group as well as restricted to those patients who were classified as having an intent to receive TIL.

DFI-1 was defined as the time from the initial diagnosis to the first metastatic recurrence at any site. DFI-2 was defined as the time from the first recurrence to the recurrence in the liver.

All *P* values are two tailed and are presented without adjustment for multiple comparisons.

RESULTS

Patient Characteristics and Operative Findings

A total of 539 patients who were enrolled onto various immunotherapy protocols had MML. Tumor procurement was performed for 204 (38%) of 539 patients with hepatic disease. Among the patients with hepatic disease as a site of metastases, 35 (17%) of 204 patients underwent procurement of the hepatic lesions. Patient demographic information, pathologic results, and operative details are listed in Table 1. Of the 35 patients, 11 (31%) of 35 patients had resection to NED, 9 (26%) of 35 of whom had never received TIL therapy (Fig. 1). The other two patients had a resection after gene therapy and were rendered NED. Twenty-four (69%) of 35 had synchronous hepatic and/or extrahepatic disease (EHD) after liver resection. Fifteen (63%) of 24 patients received postoperative TIL, and 7 (29%) of 24 did not receive postoperative TIL. The other 2 (8%) of 24 patients had postoperative gene therapy.

Ninety-seven percent of the patients received preoperative systemic therapy, and all had progressive disease other than the two patients who were resected to NED after gene therapy. No patients were treated specifically with neoadjuvant therapy with intent to undergo an operation. Rather, all systemic therapy was administered to treat metastatic disease as the primary modality. Patients who were resected to NED and who received or did not receive TIL did not greatly differ in terms of systemic therapy including chemotherapy, IL-2, vaccination, or gene therapy. One (2.9%) of 35 patients died within 30 days after liver resection. This patient was discharged on postoperative day 4 without complications after a left-lateral sectionectomy, readmitted on postoperative day 12 for IL-2 therapy, and died on postoperative day 20 from complications of IL-2. He had rapidly progressive disease in multiple organs confirmed on autopsy.

Clinical Outcomes and Prognostic Factors

For the entire group of 35 patients, the 3-year actuarial survival was 53% with a median OS of 3.0 years (1 month to 16.4 years) (Fig. 2). Although the absence of EHD ($P = .026$), negative margin at resection ($P = .056$), and a single hepatic metastasis ($P = .04$) approached statistical significance, no factors were statistically significant with respect to association with survival when adjusted for multiple comparisons. Only EHD was independently associated with survival when evaluated in a Cox model (hazard ratio, 4.77; 95% confidence interval on hazard ratio, 1.05–21.67; $P = .043$).

Given the complexities of the variation in patients included in this report, the subgroups of the 35 patients will now be reviewed independently as the patients who were resected to NED and as the patients who underwent resection with the intent to receive TIL.

Nine patients were resected to NED and did not receive TIL. Clinicopathologic features were recorded but not analyzed as a result of the small number of patients. Of note, one (11%) of nine patients had EHD that was resected with a simultaneous pulmonary metastasectomy. All nine patients had a solitary hepatic metastasis. The median DFI-1 was 1.4 years (0–10.3 years) and the median DFI-2 was 0 years (0–6.3 years). The actuarial 3-year survival was 80% with median OS that had not been reached (Fig. 3). Four (44%) of nine patients experienced recurrence of disease and had a median disease-free survival of 14 months. One patient had a recurrence in the liver that was treated by radiofrequency ablation and remained NED 6 months after this procedure. Another patient had a recurrence in the periportal lymph nodes that was resected and remained NED 8 years after the second operation. Of these nine patients, seven remained NED, and two had died of disease.

Twenty-four patients underwent liver resection with the intent to receive postoperative TIL. All 24 patients had residual disease after liver resection. Two patients received postoperative gene therapy and were excluded from this analysis. No factors reached significance.

Of the 24 patients who had residual disease after liver resection, 23 (96%) had EHD. The one patient without EHD had extensive liver involvement and a nonanatomic wedge resection was performed to collect tumor for TIL. Eighteen (75%) of the 24 patients had more than two hepatic lesions. The median DFI-1 was 1.0 year (range, 0–8.5 years), and the DFI-2 was .1 year (0–6.3 years). The 3-year actuarial survival was 51% with a median OS that had not been reached (0.1–16.4+ years).

Fifteen (63%) of 24 patients received postoperative TIL. Thirteen (87%) of these 15 patients received TIL from the hepatic lesion. One patient had hepatic TIL that was non-reactive and had a repeat TIL collected from a mandibular lymph node that yielded reactive TIL. The other patient underwent a simultaneous splenectomy and the lymphocytes from the spleen were used for TIL infusion. The actuarial 3-year survival was 65% and the median OS had not been reached (Fig. 4). The 3-year actuarial survival of the 13 patients who received TIL from the liver resection was 63% which is similar to that resulting from inclusion of the two patients who received TIL from other lesions. The median PFS after hepatic resection and TIL therapy was 10 months (range, 3–197+ months). Six (40%) of the 15 patients experienced objective responses with four PRs and 2 (13%) complete responses (CR). Four (27%) of 15 of these patients had not experienced progression including both patients with a CR; the median follow-up for these patients was 55 months (range, 42–197 months).

Seven (29%) of 24 patients underwent resection with the intent to receive TIL but did not receive therapy. Four patients did not receive TIL because the TIL were nonre-active, one patient had progressive disease in the brain, one patient had severe coronary artery disease, and one patient died while receiving IL-2 (the only postoperative death). The median survival of these seven patients was 4.6 months, and only one patient survived for >1 year (Fig. 5). The median PFS after liver resection was 2 weeks.

DISCUSSION

Liver resection to procure TIL has resulted in prolonged survival for a highly selected group of patients with MML. This series represents the largest single institution experience with hepatic resections for melanoma. Thirty-five patients had hepatic resections. Although 11 patients had all disease resected, this series is unique in that most patients did not undergo hepatectomy to be rendered NED or to palliate symptoms. Rather, most patients had resections for the procurement of TIL.

Nine patients were rendered NED after the operation and never received TIL. This group is the most similar to published reports of metastasectomy of MML. Rose et al. presented 24 patients who had hepatic resections for MML.¹⁰ The 3- and 5-year actuarial survivals were 41% and 29%, respectively. A longer DFI (58 months vs. 35 months), only one or two hepatic lesions (92%), and no residual disease approached significance for survival. Pawlik et al. reported that 16 patients with primary ocular melanoma had 2- and 5-year actuarial survivals of 61.5% and 20.5%, respectively.¹¹ The 24 patients with primary cutaneous melanoma had 2- and 5-year actuarial survivals of 47.7% and 0%. No clinicopathologic features were deemed statistically significant for the entire group, although the patients with cutaneous primary who received chemotherapy had a statistically significant survival advantage. As they mentioned, this difference may exist because patients survived long enough to receive chemo-therapy. In addition, the patients who had synchronous EHD fared poorly, with a median survival of 2.8 months.

In our study, nine patients had resection of all disease. The patients did experience long-term survival, but whether resection affected survival is uncertain. The association between the operation and the outcome may be due to unidentified factors other than the operation itself. In addition, the 9 (1.7%) of 539 patients whose disease was resected indicate that complete removal of metastatic disease is rare. Although prognostic factors were not analyzed in this group because of the small number of patients, all patients had one hepatic metastasis, and all but one patient had disease isolated to the liver. One hepatic lesion and no residual disease were consistent with the favorable characteristics as reported by Rose et al.¹⁰ Interestingly, two patients were rendered NED by a second intervention after a recurrence and fared well (remained NED at 6 months and 8 years). The experience at our institution, as well as in other reports, did not prove that the patients experienced prolonged survival as a result of the operation, yet the patients survived much longer than historical controls of patients with MML. None of these reports have a control cohort, but the reports do suggest that patients with disease isolated to the liver may benefit from surgery. Although the patients who underwent an operation were highly selected, we recommend that patients should undergo surgical evaluation, especially with one lesion and no EHD.

The unique group of patients are the 24 who underwent hepatic resection with the intent to treat with TIL. No comparisons exist in the literature. Because the administration of TIL has resulted in the highest reported objective response rates for melanoma, even major operations such as hepatic resections are reasonably justifiable to generate this therapy.²⁵ In addition, multiple reports of metastatic disease have demonstrated that hepatic resection can

be performed safely. In this series, one death occurred within 30 days, but the patient died during IL-2 therapy after an uneventful recovery from the operation.

Twenty-two of the 24 patients were analyzed for prognostic factors (Fig. 1). Two of the 24 patients were excluded from analysis because they had received postoperative gene therapy. No prognostic factors were identified as statistically significant. The patients who would receive postoperative TIL were not known at the time of operation; therefore, TIL was not a prognostic factor. Yet the administration of TIL was clearly associated with longer survival, although with potential bias because other characteristics may distinguish these patient groups (Figs. 4 and 5). The cohort of 22 patients had a 3-year actuarial survival of 51%, but the 15 patients who received postoperative TIL had a 3-year actuarial survival of 65%. This survival was not too different from the 80% 3-year survival of the patients resected to NED. The survival and duration of response are unprecedented for MML to any visceral organ. Most importantly, four of the responding patients had sustained a durable response without recurrence or progressive disease with follow-up of 3.3 years to 16.4 years. Our results revealed that patients who undergo hepatic resection for the procurement of TIL have a reasonable expectation for a response that may be ongoing for years.

These patients did not have the same selection bias present for patients resected to NED. The patients had multiple hepatic and extrahepatic lesions (Table 2). The survival of patients with MML and synchronous MML to extrahepatic sites is as poor as disease in any other organ.² In this cohort, >80% of the patients had more than two hepatic lesions. The DFI-1 was 1.0 years and the DFI-2 was .1 years, which was much shorter than reported for patients undergoing resection. Although patients had to be able to tolerate an operation and to continue to postoperative therapy, this group fared much better than the cohort that did not receive postoperative TIL.

The seven patients who did not receive postoperative TIL had a median survival of 4.6 months. This survival is nearly identical for patients with hepatic metastases who never underwent liver resection, as previously published.^{4,5} The outcome of this cohort suggests that patients who undergo hepatic resection with residual disease and without subsequent TIL therapy have a dismal prognosis. These patients did not benefit from the operation. The patients did much worse without postoperative TIL therapy even though both groups seemed similar on the basis of analysis of all clinicopathological features. Granted, failure to detect a difference when one exists is a distinct possibility with groups of this size, but most patients were not excluded as a result of progressive disease or declined in performance status. Rather, the TIL cells were nonreactive. If the patients had reactive cells, they may have received treatment. This finding supports the notion that TIL therapy may greatly influence survival. It is possible, however, that patients with tumor that generates TIL in vitro have a better prognosis whether or not they receive TIL.

Several limitations of this study exist. First, it is a retrospective review. Second, on the basis of both referral patterns as well as length of treatments, a selection bias may exist for patients who have a longer disease-specific survival, which may reflect a more favorable biology. The patients unable to receive TIL may have had more aggressive disease that precluded effective therapy, and even if they had TIL, they may have done poorly. Although

the outcome of the entire group was reported, the subgroups are vastly different, requiring separate analyses that resulted in small cohorts. Despite these limitations, this study is the largest single-institution report of liver resections for MML, and several patients have had durable responses when treated with surgery to obtain tissue for TIL therapy. In addition, liver resection in this patient population is feasible without undue risk despite advanced disease.

Among patients who have isolated MML and no EHD, complete resection may be considered because it might be a beneficial intervention in a selected group of patients. Hepatic resection to generate TIL therapy may result in prolonged survival. Even in the presence of hepatic and synchronous EHD, if the patients proceed to TIL therapy after operation, durable responses can be obtained. From these data, it is not unreasonable to conclude that TIL therapy might prolong survival. Given these results, when hepatic resection is the only option to generate TIL, it is reasonable for patients with MML to undergo resection.

ACKNOWLEDGMENT

National Institutes of Health National Cancer Institute, Intramural grant, provided support for the Surgery Branch, Immunotherapy Section.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71–96. [PubMed: 18287387]
2. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19:3622–34. [PubMed: 11504744]
3. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001;19:3635–48. [PubMed: 11504745]
4. Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg*. 1995;181:193–201. [PubMed: 7670677]
5. Leiter U, Meier F, Schittek B, Garbe C. The natural course of cutaneous melanoma. *J Surg Oncol*. 2004;86:172–8. [PubMed: 15221923]
6. Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. *Ann Surg*. 1998;228:307–19. [PubMed: 9742914]
7. Li Y, McClay EF. Systemic chemotherapy for the treatment of metastatic melanoma. *Semin Oncol*. 2002;29:413–26. [PubMed: 12407507]
8. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multi-center randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol*. 1999;17:2745–51. [PubMed: 10561349]
9. Ahmann DL, Creagan ET, Hahn RG, et al. Complete responses and long-term survivals after systemic chemotherapy for patients with advanced malignant melanoma. *Cancer*. 1989;63:224–7. [PubMed: 2642731]
10. Rose DM, Essner R, Hughes TM, et al. Surgical resection for metastatic melanoma to the liver: the John Wayne Cancer Institute and Sydney Melanoma Unit experience. *Arch Surg*. 2001;136:950–5. [PubMed: 11485537]
11. Pawlik TM, Zorzi D, Abdalla EK, et al. Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. *Ann Surg Oncol*. 2006;13:712–20. [PubMed: 16538410]

12. Herman P, Machado MA, Montagnini AL, et al. Selected patients with metastatic melanoma may benefit from liver resection. *World J Surg.* 2007;31:171–4. [PubMed: 17171491]
13. Karakousis CP, Velez A, Driscoll DL, Takita H. Metastasectomy in malignant melanoma. *Surgery.* 1994;115:295–302. [PubMed: 8128354]
14. Wong SL, Coit DG. Role of surgery in patients with stage IV melanoma. *Curr Opin Oncol.* 2004;16:155–60. [PubMed: 15075909]
15. Reddy SK, Barbas AS, Marroquin CE, et al. Resection of noncolorectal nonneuroendocrine liver metastases: a comparative analysis. *J Am Coll Surg.* 2007;204:372–82. [PubMed: 17324770]
16. Papachristou DN, Fortner JJ. Surgical treatment of metastatic melanoma confined to the liver. *Int Surg.* 1983;68:145–8. [PubMed: 6885293]
17. Ollila DW, Morton DL. Surgical resection as the treatment of choice for melanoma metastatic to the lung. *Chest Surg Clin N Am.* 1998;8:183–96. [PubMed: 9515181]
18. Ollila DW, Essner R, Wanek LA, Morton DL. Surgical resection for melanoma metastatic to the gastrointestinal tract. *Arch Surg.* 1996;131:975–9;979–80. [PubMed: 8790168]
19. Mondragon-Sanchez R, Barrera-Franco JL, Cordoba-Gutierrez H, Meneses-Garcia A. Repeat hepatic resection for recurrent meta-static melanoma. *Hepatogastroenterology.* 1999;46:459–61. [PubMed: 10228842]
20. Foster JH. Survival after liver resection for secondary tumors. *Am J Surg.* 1978;135:389–94. [PubMed: 626320]
21. Branum GD, Epstein RE, Leight GS, Seigler HF. The role of resection in the management of melanoma metastatic to the adrenal gland. *Surgery.* 1991;109:127–31. [PubMed: 1992544]
22. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg.* 2006;244: 524–35. [PubMed: 16998361]
23. Rosenberg SA. The emergence of modern cancer immunotherapy. *Ann Surg Oncol.* 2005;12:344–6. [PubMed: 15843873]
24. Rosenberg SA, Restifo NP, Yang JC, et al. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. *Nat Rev Cancer.* 2008;8:299–308. [PubMed: 18354418]
25. Dudley ME, Yang JC, Sherry R, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol.* 2008;26:5233–9. [PubMed: 18809613]
26. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol.* 2005;23:2346–57. [PubMed: 15800326]
27. Dudley ME, Wunderlich JR, Robbins PF, et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. *Science.* 2002;298(5594):850–4. [PubMed: 12242449]

FIG. 1.

Flow diagram of patients who underwent liver resections for metastatic melanoma (MML). Patients are classified on the left arm as being resected to NED and classified on the right arm having residual metastatic disease after resection of liver TIL. NED, no evidence of disease; TIL, tumor-infiltrating lymphocytes. Patients underwent liver resections for MML at the National Cancer Institute, National Institutes of Health

FIG. 2.

Overall survival of the 35 patients who underwent hepatic resection of metastatic melanoma to the liver. The actuarial 3- and 5-year survivals plateau at 53%. Eleven of the 35 patients had all disease resected, whereas 24 patients had residual disease after the operation. Among the 24 patients with residual disease, 15 patients received tumor-infiltrating lymphocyte (TIL) therapy, 2 patients had postoperative gene therapy, and 7 patients did not receive postoperative therapy

FIG. 3.

Overall survival of the patients who had all disease resected at the time of the liver operation. The actuarial 3- and 5-year survivals plateau at 80%. Eight patients had disease isolated to the liver, and one patient had a synchronous pulmonary metastasectomy

FIG. 4.

Overall survival of the patients ($n = 15$) with residual disease at the time of hepatic resection who received postoperative tumor-infiltrating lymphocyte therapy. The actuarial 3- and 5-year survivals plateau at 65%

FIG. 5.
Overall survival of the 7 patients who did not receive tumor-infiltrating lymphocyte therapy.
Median survival was 4.6 months

TABLE 1

Clinical and pathologic characteristics of 35 patients who underwent liver resection for metastatic melanoma

Characteristic	Value
Feature	
Age, median (range) at diagnosis (y)	41 (17–60)
Age, median (range) at operation (y)	44 (26–66)
Sex, M/F	24/11
AJCC stage, n (%)	
I/II	12 (35%)
III	16 (47%)
IV	5 (15%)
Unknown	1 (3%)
Pathology, n (%)	
Cutaneous	29 (83%)
Ocular	1 (3%)
Unknown primary	5 (14%)
DFI	
DFI-1 (mo), median (range)	17 (0–124)
DFI-2 (mo), median (range)	0 (0–76)
Hepatic resection, n (%)	
Nonanatomic resection	10 (29%)
Anatomic resection	25 (71%)
Laparoscopic	10 (29%)
Open	25 (71%)
Left lateral sectionectomy	5 (14%)
Wedge resection	8 (23%)
Segmentectomy	13 (37%)
Left hepatectomy	2 (6%)
Left trisectionectomy	1 (3%)
Right hepatectomy	3 (9%)
Bisegmentectomy	2 (6%)
Posterior sectionectomy	1 (3%)
Reoperation	3 (9%)
No. of metastases, n (%)	
1	15 (43%)
2	1 (3%)
>2	19 (54%)
Synchronous extrahepatic metastases, n (%)	24 (69%)
Free of disease after resection, n (%)	11 (31%)

AJCC American Joint Committee on Cancer, *DFI* disease-free interval

TABLE 2

Extrahepatic disease sites and remaining liver disease among 24 patients undergoing liver resections for metastatic melanoma

Patient	Liver	Lung	Viscera ^a	Brain	Bone	Lymph node	Soft tissue
1	X					X	
2	X	X					
3	X						X
4		X					
5	X						
6	X	X					
7						X	
8		X					X
9		X	X				
10	X	X					
11			X				X
12	X	X			X		
13	X	X	X				
14						X	
15		X	X				
16		X				X	
17		X	X		X		X
18			X				
19	X	X	X				
20	X		X				
21	X					X	
22	X	X	X	X	X		
23	X	X					
24	X	X	X				

^aViscera indicates heart, spleen, kidney, gastrointestinal tract, and pancreas