European Journal of Cancer 103 (2018) 24–31

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The impact of effective systemic therapies on surgery for stage IV melanoma

M.J.F. Smith*,[1], H.G. Smith [1], K. Joshi, M. Gore, D.C. Strauss, A.J. Hayes, J. Larkin

The Melanoma Unit, The Royal Marsden Hospital NHS Foundation Trust, UK

Received 13 July 2018; accepted 2 August 2018

KEYWORDS
Stage IV melanoma;
Immunotherapy;
Surgery;
Metastasectomy

Abstract ***Introduction:*** The outcomes of patients with metastatic melanoma have significantly improved with the introduction of effective systemic therapies (ESTs). The role of surgery in the context of ESTs for stage IV melanoma is evolving. We sought to characterise the changing patterns of surgery and oncological outcomes in patients with stage IV melanoma treated before and after the establishment of ESTs.
Methods: Patients undergoing surgical resection of stage IV melanoma were identified from our institutional database from 2003 to 2015. Patients were grouped into two cohorts, those referred before EST (2003–2007) and after EST (2011–2015). Clinicopathological variables, patterns of surgery and oncological outcomes in the two groups were compared.
Results: A total of 138 patients underwent surgery for stage IV melanoma ($n = 69$ in each cohort). We observed no significant difference in the ratio of operations/patients performed. However, the pattern of operations altered, with a significant decrease in in-transit excisions (0.9% vs. 19.4%, $p < 0.001$) and an increase in abdominal metastasectomies (21.1% vs. 4.2%, $p < 0.001$), in the after-EST cohort. Novel indications for surgical intervention were noted in the after-EST cohort, with a significant increase in potentially curative operations for residual oligometastatic disease (15.9% vs. 4.3%, $p = 0.045$). Survival after surgery was prolonged in the after-EST cohort (median 16 months vs. 6 months, $p < 0.001$), with the stage at initial metastasectomy (stage 4a, hazard ratio [HR] 0.45 (0.28–0.73), $p = 0.001$) and treatment with immune checkpoint inhibitors (HR 0.38 (0.25–0.60), $p < 0.001$) associated with prolonged survival.
Discussion: Surgery remains important in the management of stage IV melanoma, with evolving indications and patterns of intervention after the introduction of ESTs. The combination of judicious surgery and EST may improve oncological outcomes.

* *Corresponding author*: The Melanoma Unit, The Royal Marsden Hospital NHS Foundation Trust, Fulham Road, London. SW3 6JJ, UK.
E-mail address: myles.smith@rmh.nhs.uk (M.J.F. Smith).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejca.2018.08.008
0959-8049/

1. Introduction

Before the advent of effective systemic therapies (ESTs), the prognosis for patients with metastatic melanoma was poor, with a median survival of approximately 7 months in patients with stage IV disease [1]. The use of traditional systemic chemotherapies, such as dacarbazine, was limited by low response rates and an inability to significantly prolong the overall survival [2,3]. Although immunomodulatory agents, such as interleukin-2 or interferon-α, showed promise in early clinical trials, and even slightly improved progression-free survival in combination with traditional chemotherapy, ultimately no improvement in the overall survival was found [4–7]. Therefore, before 2011, there was no convincing evidence that systemic therapies could significantly prolong survival in stage IV melanoma.

In this setting of limited systemic treatment options, surgical intervention for stage IV melanoma was performed with one of the two distinct indications. First, in patients with disseminated disease, surgery was an effective palliative treatment and, although offering no survival benefit, achieved symptom resolution in the majority of patients [8,9]. Second, surgery was performed with curative intent in patients with limited or oligometastatic disease. With the belief that metastatic potential evolves through intermediary states, patients with indolent and resectable lesions were selected for surgery, the rationale being that the metastatic cascade may be interrupted before widespread dissemination occurred [10,11]. In retrospective series, surgery in such patients was consistently associated with improved survival outcomes compared with patients managed non-operatively or those operated on with palliative intent [8,12,13]. Further insights into the potential benefits of surgical resection may be found in prospective studies, such as the SWOG S9430, MSLT-I and MMAIT-IV studies [14–16]. While each of these studies is limited by a lack of adequate controls and a selection bias towards patients who have disease favourable for resection and are fit enough to undergo surgery, there is substantial evidence to support a benefit for metastasectomy in appropriately selected patients.

With the advent of ESTs, the prognosis for metastatic melanoma has markedly improved in recent years. Monoclonal antibodies targeting receptors involved in the modulation of T-cell activation pathways, such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1), have been shown to be markedly more effective than traditional systemic therapies [17,18]. More impressively, these agents appear to be capable of inducing durable responses even after the treatment has ceased, with 3-year survival of 25% with ipilimumab, a CTLA-4 inhibitor, and 40% with pembrolizumab, a PD-1 inhibitor [19,20]. Furthermore, combination of both CTLA-4 and PD-1 inhibitors augments the efficacy of these therapies, albeit at the cost of increased toxicities [21].

The impact of improved outcomes on this patient group on the indications for surgery in stage IV melanoma has only recently begun to be described [22,23]. What is becoming clear, however, is that the decision of when to operate in these patients is becoming increasingly complex. The purpose of this study was to investigate the impact of ESTs for metastatic melanoma on the indications for and outcomes after surgery for stage IV disease at our institution.

2. Methods

Patients treated at The Royal Marsden Hospital NHS Foundation Trust who had surgery for stage IV melanoma for any indication, as defined by the AJCC 7th edition classification, were identified retrospectively from electronic medical records. Two cohorts of patients were defined: a before-EST cohort (before-EST) and an after-EST cohort (after-EST). The before-EST cohort included patients referred between January 2003 and January 2007. The after-EST cohort included patients referred between January 2011 and January 2015.

Variables of interest included patient demographics; the site and thickness of the primary tumour; treatment with systemic therapies; indication for the first metastasectomy; the total number of metastasectomies and oncological outcomes. The indications for the first metastasectomy were stratified into palliative and potentially curative procedures. Both elective and emergent surgical interventions were included.

Oncological outcomes of interest included progression-free survival and overall survival. Progression-free survival was defined as the time from the initial metastasectomy until the appearance of a new lesion, progression of an existing lesion, the date of death or the date of the last follow-up. Overall survival was defined as the time from the initial metastasectomy until the date of death or the date of the last follow-up. Two-year progression-free survival and overall survival were calculated using the Kaplan–Meier method and compared using the log-rank test.

Univariable analysis with the Cox proportional hazards model was used to determine if the following factors were prognostic of survival after the initial metastasectomy: age; gender; stage at the initial metastasectomy; the total number of metastasectomies; treatment with chemotherapy; treatment with immunotherapy and treatment with targeted therapy. These variables were then combined using backwards stepwise selection methods in a multivariable analysis. The results of these analyses are presented as hazard ratios with 95% confidence intervals. All statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, New York, United States of America).