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ORIGINAL ARTICLE – MELANOMA

The Prognosis and Natural History of In-Transit Melanoma Metastases at a High-Volume Centre

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ABSTRACT

Background. Patients with in-transit melanoma metastases (ITM) experience a diverse spectrum of clinical presentations and a highly variable disease course. There is no standardized treatment protocol for these patients due to the limited data comparing treatment modalities for ITM. This is the first study to describe the disease trajectory and natural history of a large cohort of patients with ITM.

Methods. A retrospective study of patients treated for ITM between 2004 and 2018 at the Peter MacCallum Cancer Centre was performed. Clinical and pathological characteristics for primary and in-transit episodes were analyzed for predictors of relapse-free survival (RFS), distant metastasis-free survival (DMFS), and melanoma-specific survival.

Results. A total of 109 patients with 303 episodes of ITM were identified: 52 (48%) females, median age 70.1 years (range 35–92). The median RFS for all episodes was 5 months (95% confidence interval [CI] 4.2–5.7). Eighty-seven percent of episodes involving isolated in-transit lesions underwent surgical excision, compared with 17% involving more than five in-transit lesions. A trend was seen between a greater number of lesions and shorter RFS ($p = 0.055$). The median DMFS was 34.8 months (95% CI 22.8–51.6). Factors associated with shorter DMFS included primary tumor thickness (hazard ratio [HR] 1.08, 95% CI 1.01–1.15; $p = 0.026$), site of primary tumor ($p = 0.008$), and BRAF mutation (HR 2.12, 95% CI 1.14–3.94; $p = 0.018$).

Conclusions. Locoregional relapse is common in patients with ITM regardless of treatment modality. Characteristics of the ITM may predict for RFS, while primary tumor characteristics remain important predictors of DMFS.

In-transit metastases (ITM) of cutaneous melanoma are locoregional recurrences confined to the superficial lymphatics. ITM are classified as stage IIIB, IIIC, or IIID by the American Joint Committee on Cancer Staging System (AJCC 8th edition), depending on regional nodal involvement, primary tumor thickness and ulceration, and have 5-year survival rates of 83%, 69%, and 32%, respectively.[1] Patients with ITM represent a heterogenous and challenging population; lesions may be cutaneous or subcutaneous, isolated or extensive, and with or without synchronous nodal disease. Patients can experience considerable morbidity due to ulceration, bleeding and infection, as well as treatment-related adverse effects.[2] Relapse-free survival

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(RFS) ranges from weeks to years depending on tumor biology and response to therapy. Progression to distant metastases occurs in 42–86% of patients.[3–5]

Definitive surgical excision remains standard of care for patients with low-volume disease.[6,7] In those with significant disease burden and frequent recurrence, locoregional approaches, including isolated limb infusion (ILI) or perfusion (ILP), intralesional therapy (including talimogene laherparepvec [T-VEC], PV-10 [10% rose bengal disodium] and others), topical therapy and radiotherapy, have yielded durable responses.[8–11] The clinical landscape has been further complicated by the introduction of new therapies, such as tyrosine kinase inhibitors and immune checkpoint inhibitors. Landmark trials have proven these systemic agents to be effective in the setting of systemic metastases, unresectable stage III disease, and as adjuvant therapy,[12–17] although no study has specifically examined the ITM population.

The complexity of ITM management has made direct comparison of treatment approaches difficult and comparative data are limited. The existing literature fails to capture an accurate picture of the outcomes achieved in current clinical practice over long disease trajectories. This study follows patients over all episodes of ITM to characterise the natural history, treatment patterns, and prognostic indicators.

METHODS

Patients were identified from the Peter MacCallum Cancer Centre positron emission tomography (PET) database, Melanoma Research Victoria database, and a clinical database following approval from the Peter MacCallum Cancer Centre Human Research Ethics Committee (18/05R). Patients with ITM (defined as intralymphatic metastases that were confined to the superficial lymphatic system located > 2 cm from the primary tumor and regional lymph node basin) treated at the Peter MacCallum Cancer Centre between January 2004 and February 2018 were included in the analyses. In order to specifically study ITM, patients were excluded if they had previous or synchronous distant metastatic disease; however, patients with previous, synchronous, or metachronous nodal metastases were included. Each locoregional relapse (ITM and/or nodal) was recorded as a discrete episode. Once distant metastases occurred, no further episodes were recorded. Patients were followed until death or last follow-up appointment.

The RFS for each episode was measured in months from the date of treatment commencement for ITM to the date of locoregional recurrence or distant metastasis, death from any cause, or final follow-up, whichever occurred first. RFS for the first episode was measured from the date of first treatment for ITM until the date of first progression. RFS was recorded for every subsequent episode, pooled with the first episode and recorded as the RFS for all episodes. Distant metastasis-free survival (DMFS) was defined as the time from treatment commencement for ITM to the date of distant metastases or final follow-up, while melanoma-specific survival (MSS) was defined as the time from treatment commencement for ITM to the date of death from melanoma. Patients without an event outcome were censored at the last date of follow-up.

Factors associated with RFS for the first episode, DMFS, and MSS were assessed using the Cox proportional hazard model, and also described using Kaplan–Meier methods. Factors associated with overall RFS for all episodes were assessed using a conditional model of the Prentice–Williams–Peterson counting process, which analyzes ordered multiple events by stratification and based on the prior number of events during the follow-up period. Potential prognostic factors in these univariable models included sex, age, primary tumor thickness, primary tumor ulceration, primary tumor site, mitoses molecular markers (BRAF, NRAS), treatment modality, number of ITM lesions, nodal involvement, surgical margins, and first disease-free interval. The multivariable model included all covariates that were significant in each univariable model; all tests were two-sided at a significance level of 0.05. Analyses were carried out using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

Between 2004 and 2018, 109 patients were identified and treated for 303 ITM episodes. Patient and primary tumor characteristics are shown in Table 1. The median age at first ITM diagnosis was 70.1 years (range 35–92). Eleven patients (10%) were sentinel lymph node biopsy (SLNB)-positive prior to ITM diagnosis, 19 patients (27%) were SLNB-negative, and 69 patients (63%) did not undergo SLNB prior to ITM diagnosis. Thirteen patients (12%) had macroscopic nodal disease prior to ITM diagnosis. A total of 24 patients (22%) had lymph node disease prior to ITM diagnosis. The median disease-free interval from the time of primary diagnosis to ITM was 13.1 months (range 0–311); the median length of follow-up was 33.7 months (range 1–141); and the median number of ITM episodes per patient was 2 (range 1–14). Ninety-two episodes (30%) involved a single in-transit lesion, 150 episodes (50%) involved two to five lesions, 53 episodes (17%) involved more than five lesions, and eight episodes

TABLE 1 Patient, primary tumor, and in-transit metastases characteristics at the time of first ITM

Characteristic	Patients
Sex	
Female	52 (48)
Male	57 (52)
Age at first ITM diagnosis, years [median (range)]	70.1 (35–92)
Primary site	
Lower limb	47 (43)
Trunk	22 (20)
Upper limb	13 (12)
Head/neck	18 (17)
Unknown	9 (8)
Breslow thickness, mm [median (range)]	3 (0.22–21)
Primary tumor ulceration	
Present	46 (42)
Absent	38 (35)
BRAF status	
Mutation	32 (29)
Wild-type	66 (61)
Unknown	11 (10)
NRAS status	23 (21)
Mutation	
Wild-type	21 (19)
Unknown	65 (60)
KIT status	
Mutation	0
Wild-type	25 (23)
Unknown	84 (77)
SLNB status at initial melanoma diagnosis	
SLNB-positive	11 (10)
SLNB-negative	29 (27)
No SLNB	69 (63)
Macroscopic nodal disease at initial melanoma diagnosis	
Yes	13 (12)
No	96 (88)
AJCC stage at initial melanoma diagnosis	
I	20 (18)
II	41 (38)
III	38 (35)
Unknown	10 (9)

Data are expressed as *n*(%) unless otherwise specified

ITM in-transit metastases, *SLNB* sentinel lymph node biopsy, *AJCC* American Joint Committee on Cancer

(3%) involved isolated nodal progression in a patient with prior ITM (Table 2). Fifty-two patients (48%) had nodal involvement at least once before the date of last follow-up (either prior to ITM development or synchronously).

Treatment Modality

Surgery was the treatment modality utilized in 211 episodes (70%), and 99 patients (91%) had surgery at least once during their treatment course (Table 2). Surgery included appropriate surgical management as assessed by the treating clinician and multidisciplinary team, and included WLE, SLNB and lymphadenectomy, depending on the type of relapse. Surgery was predominately used in episodes involving either a single or two to five ITM. In treatment episodes involving more than five ITM, intralesional injection and ILI were more commonly used (Table 2). ILI was performed in 14 patients and was used as the first-line treatment for five patients; ILI is the only regional therapy performed at this institution. When not used as first-line therapy, the median number of episodes prior to ILI treatment was three (range 1–7). In all cases in the current series, intralesional treatment involved PV-10. Systemic therapy was used as the first-line treatment in four patients. When not used as the first-line therapy, the median number of episodes prior to commencement of treatment with systemic therapy was three (range 1–5). Systemic agents used included dabrafenib/trametinib, atezolizumab/cobimetinib, ipilimumab and pembrolizumab. Systemic therapy was not given in combination with other therapies, or as adjuvant therapy.

First Episode

In the first episode of ITM, 44 patients (40%) had a single lesion, 54 patients (50%) had two to five lesions, and 11 patients (10%) had more than five lesions. Therapy for the first presentation of ITM involved surgery in 92 patients (84%), radiotherapy in two patients (2%), systemic therapy in four patients (4%), intralesional injection in six patients (5%), and ILI in five patients (5%) [electronic supplementary Table S1]. Following the first presentation of ITM, 68 patients (62%) developed further locoregional disease as the next site of relapse, 23 patients (21%) developed distant metastases, and 18 patients (17%) had no progression. Eighteen patients (17%) remained disease-free following a single episode of ITM, and 23 patients (21%) developed distant metastases following a single ITM episode.

Relapse-Free Survival (RFS) for the First Episode

The median duration of RFS following the first ITM treatment was 6.5 months (95% confidence interval [CI] 5.1–8.4). Twelve-month RFS following the first ITM treatment was 37% (95% CI 27–47) for patients treated with surgery and 10% (95% CI 3–34) for those who had non-surgical treatment ($p = 0.018$) (Fig. 3c). At

TABLE 2 Treatment modality according to the number of in-transit lesions

	Number of lesions				
Treatment modality for ITM	All episodes	1	2–5	> 5	Nodal only[a]
Total	303 (100)	92 (30)	150 (50)	53 (17)	8 (3)
Surgery	211 (70)	80 (87)	116 (77)	9 (17)	6 (75)
Radiotherapy	15 (5)	1 (1)	7 (5)	6 (11)	1 (13)
Systemic therapy	22 (7)	6 (7)	9 (6)	7 (13)	0
Intralesional	34 (11)	2 (2)	13 (9)	18 (34)	1 (13)
ILI	14 (5)	0	4 (3)	10 (19)	0
Topical	7 (2)	3 (3)	1 (1)	3 (6)	0

Data are expressed as *n*(%)

Treatment modalities used in all 303 episodes of ITM for 109 patients; this is further stratified by the number of ITM lesions

[a]Indicates nodal progression, does not include nodal involvement at the time of the primary diagnosis

ITM in-transit metastases, *n* sample size, *ILI* isolated limb infusion

12 months, a higher proportion of patients with two to five or more than five ITM relapsed compared with patients with one ITM ($p = 0.035$) (Fig. 3a). On multivariable analysis, no factors were significant predictors of RFS following the first ITM episode.

RFS for All Episodes

A further analysis was performed considering all 303 episodes of ITM. The median duration of RFS for all episodes was 5 months (95% CI 4.2–5.7). The median duration of RFS decreased with subsequent ITM episodes; the interval following the first episode was 6.51 months (95% CI 4.9–8.4), 4.6 months (95% CI 3.3–6.1) following the second episode, and 4.21 months (95% CI 2.4–5.6) following the third episode. Univariable analysis of RFS across all episodes demonstrated an association between non-surgical treatment and shorter RFS (hazard ratio [HR] 1.38, 95% CI 1.04–1.83; $p = 0.026$). Furthermore, an association was demonstrated between the five treatment modalities utilized when compared with surgery ($p < 0.001$): intralesional injection (HR 2.60, 95% CI 1.68–4.04), ILI (HR 1.92, 95% CI 1.15–3.20), radiotherapy (HR 1.04, 95% CI 0.57–1.90), systemic therapy (HR 0.57, 95% CI 0.36–0.91), and topical agents (1.00, 95% CI 0.42–2.39). However, treatment modality was not included on multivariable analysis due to collinearity. Multivariable analysis of RFS across all ITM episodes showed a trend of earlier recurrence with the greater number of lesions (two to five: HR 1.21, 95% CI 0.82–1.77; more than five: HR 1.79, 95% CI 1.10–2.93; $p = 0.055$) (Fig. 2a). The multivariable analysis did not find an association between any primary tumor characteristic and RFS (Fig. 2a). The multimodal treatment course and relapse-free intervals for patients with more than one episode of ITM (62% of the cohort) are represented in Fig. 1.

Distant Metastasis-Free Survival

The median duration of DMFS in all patients was 34.8 months (95% CI 22.8–51.6). Factors associated with a shorter DMFS included greater Breslow thickness of primary tumor (HR 1.08, 95% CI 1.01–1.15; $p = 0.026$), site of the primary tumor compared with lower limb (head: HR 4.71, 95% CI 1.94–11.46; trunk: HR 1.85, 95% CI 0.86–3.98; upper limb: HR 1.80, 95% CI 0.64–5.03; $p = 0.008$), and BRAF mutation (HR 2.12, 95% CI 1.14–3.94; $p = 0.018$) (Fig. 2b). No significant association with DMFS was found for the number of ITM lesions (Fig. 3b) or ITM treatment modality (Fig. 3d). Univariable analysis of DMFS demonstrated that nodal involvement (prior or synchronous) was associated with shorter DMFS (HR 2.56, 95% CI 1.46–4.47; $p = 0.001$).

Final Status

At time of final follow-up, 30 patients (27%) were relapse-free, 16 patients (15%) had locoregional disease, 37 patients (34%) had distant metastases, and 21 patients (19%) had died due to melanoma and five patients (5%) had died due to other causes.

Melanoma-Specific Survival

The median MSS was not reached. Breslow thickness was the only factor that was associated with a shorter MSS on multivariable analysis (HR 1.11, 95% CI 1.01–1.22; $p = 0.029$) (Fig. 2c). Univariable analysis of MSS

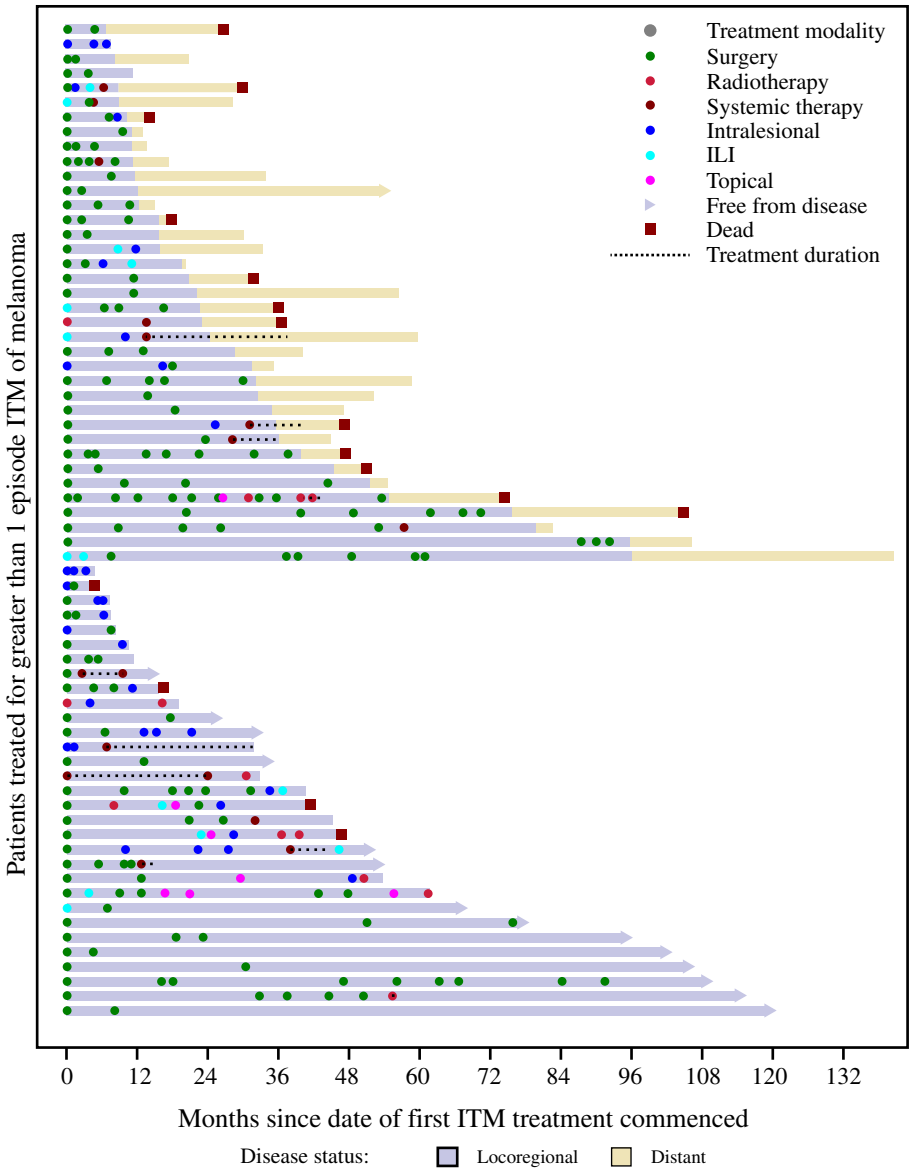

FIG. 1 Heterogeneity of in-transit disease. Swimmer plot of all patients with more than one ITM episode, grouped by disease status, with the upper half of the plot demonstrating patients with distant relapse and the lower half showing patients without distant metastases. All treatment episodes and types are shown. Patients are followed through all locoregional episodes until distant metastasis or final follow-up. *ITM* in-transit metastases, *ILI* isolated limb infusion

demonstrated that nodal involvement was associated with shorter MSS (HR 3.06, 95% CI 1.19–7.83; $p = 0.020$).

DISCUSSION

There is a paucity of data regarding the outcomes of patients with ITM followed over multiple ITM episodes. The majority of studies examine the factors that predict the development of the first episode of ITM but not subsequent relapse. The complexity of disease trajectories with multiple recurrences and treatments remains a challenge for those treating and studying patients with ITM. This has also been our experience, as demonstrated in Fig. 1, in which we observed a range of treatment pathways, relapse-free intervals, and outcomes. A median RFS of 5 months across all episodes, and the experience of relapse in 83% of patients, confirms that recurrence is common in this population. However, the median DMFS of 34.8 months is comparable to the existing literature and highlights the indolent pattern of multiple locoregional relapses.[18] A minority of patients (21%) developed distant metastases after the first episode of ITM, reflecting a more aggressive tumor biology. A longer interval of RFS was observed following the first episode of ITM compared with the second and third episodes, demonstrating a trend of poorer prognosis with increasing number of relapses.

Increasing numbers of ITM lesions predicted for locoregional recurrence but did not predict for distant relapse, a finding that has not been addressed in previous studies.[3–5] Multivariable analysis demonstrated that having two to five ITM was associated with a higher risk of relapse across all episodes compared with having one ITM; this

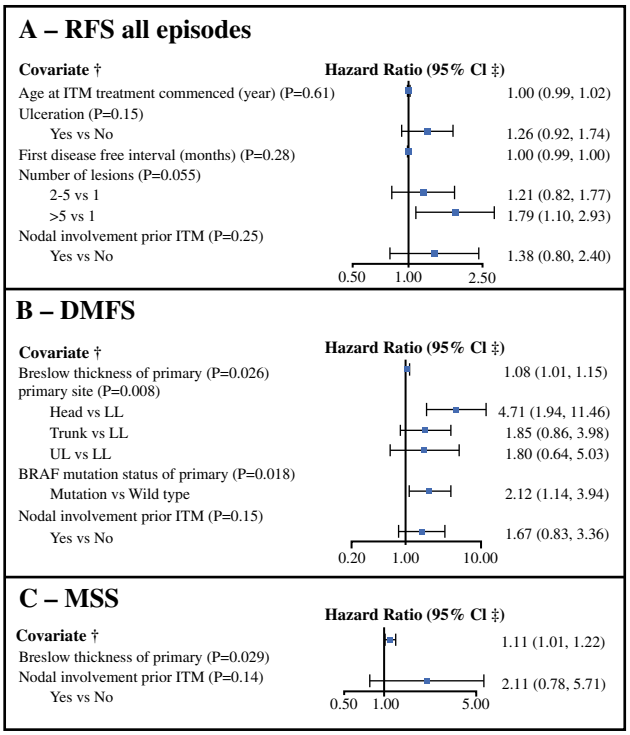

FIG. 2 Multivariable analyses of factors associated with survival. Factors associated with survival (multivariable analysis) demonstrating **a** RFS for all episodes based on the Prentice–Williams–Peterson counting process total time model with common effects; **b** DMFS for all patients based on the Cox proportional hazard model; and **c** MSS for all patients based on the Cox proportional hazard model. *ITM* in-transit metastases, *CI* confidence interval, *RFS* relapse-free survival, *DMFS* distant metastasis-free survival, *MSS* melanoma-specific survival, *LL* lower limb, *UL* upper limb, † indicates last reference group, ‡ indicates Wald confidence limits

risk was shown to be greater still in the more than five ITM group. The number of lesions was not associated with DMFS or MSS, which highlights the important biological difference between locoregional disease (representing dissemination via lymphatics) compared with distant metastases (representing hematogenous spread).[19]

Fifty-two percent of patients had nodal disease at least once throughout their disease trajectory, either prior to ITM or synchronously. Patients with nodal involvement at any stage of their disease course had a shorter RFS (all episodes), DMFS, and MSS on univariable analysis. These findings are consistent with the 8th AJCC staging system and other literature that allocates a higher stage for patients with both nodal and in-transit disease.[1,3,18]

The main determinants of DMFS were the primary tumor characteristics, including Breslow thickness, site, and mutation status. The presence of an actionable BRAF mutation was associated with a 2.12-fold increased risk of distant metastasis. It has been previously established that BRAF mutation is associated with poorer prognosis in stage III melanoma, although these patients may potentially achieve improved outcomes with combination tyrosine kinase inhibitor therapy compared with their non-BRAF-mutant counterparts.[20,21] No other molecular markers (NRAS and KIT) were found to be associated with any outcome analyzed.

A number of previous studies have also demonstrated the dominant prognostic relevance of primary tumor characteristics, even after the development of ITM.[4,5,18,22] This is consistent with the AJCC 8th edition, where primary tumor thickness and ulceration are used to stratify stage III groups.[1]

Surgical excision remains the first-line treatment for ITM patients with a low to moderate number of lesions. There was a 1.38-fold increased risk of relapse across all episodes with non-surgical treatment, although due to collinearity with the number of lesions, this was excluded from the multivariable analysis. A higher risk of relapse compared with surgery was associated with intralesional injection, ILI, radiotherapy, and topical agents, likely reflecting their use in more advanced disease. Only systemic therapy had a lower risk of relapse compared with surgery on univariable analysis. Individual modalities, other than surgery, were not included on multivariable analysis of overall RFS due to the small sample size relative to surgery. Promising findings with the use of systemic therapy indicate the need for further studies investigating the role of these therapies in this population, especially given the underrepresentation of ITM patients in recent trials including unresectable stage III patients.[15–17] In recent years, there has been an increase in the use of BRAF/MEK inhibitors and immune checkpoint inhibitors in stage III melanoma; the low number of patients in this study treated with these agents may be due to these agents not being available to many patients at the time of their treatment. Adjuvant therapy was not used routinely, and minimal data exist in the literature to inform the role of adjuvant systemic therapy following surgery for ITM. Key reports from trials examining adjuvant combination dabrafenib/trametinib, as well as the CheckMate-238 trial comparing ipilimumab with nivolumab, did not perform subgroup analyses for ITM patients, while the KEYNOTE-054 trial (pembrolizumab) excluded the ITM population altogether.[12–14] The current study demonstrates an increased risk of relapse in patients undergoing ILI compared with surgical excision, although ILI was most commonly reserved for high burden disease and second-line therapy. Extensive literature has consistently demonstrated high response rates and durable responses.[11,23,24] Intralesional injection in the current series only included PV-10, which does not represent the experience at other centers that may use different injectable agents. No previous studies have directly compared non-surgical modalities with surgery, however these results are limited

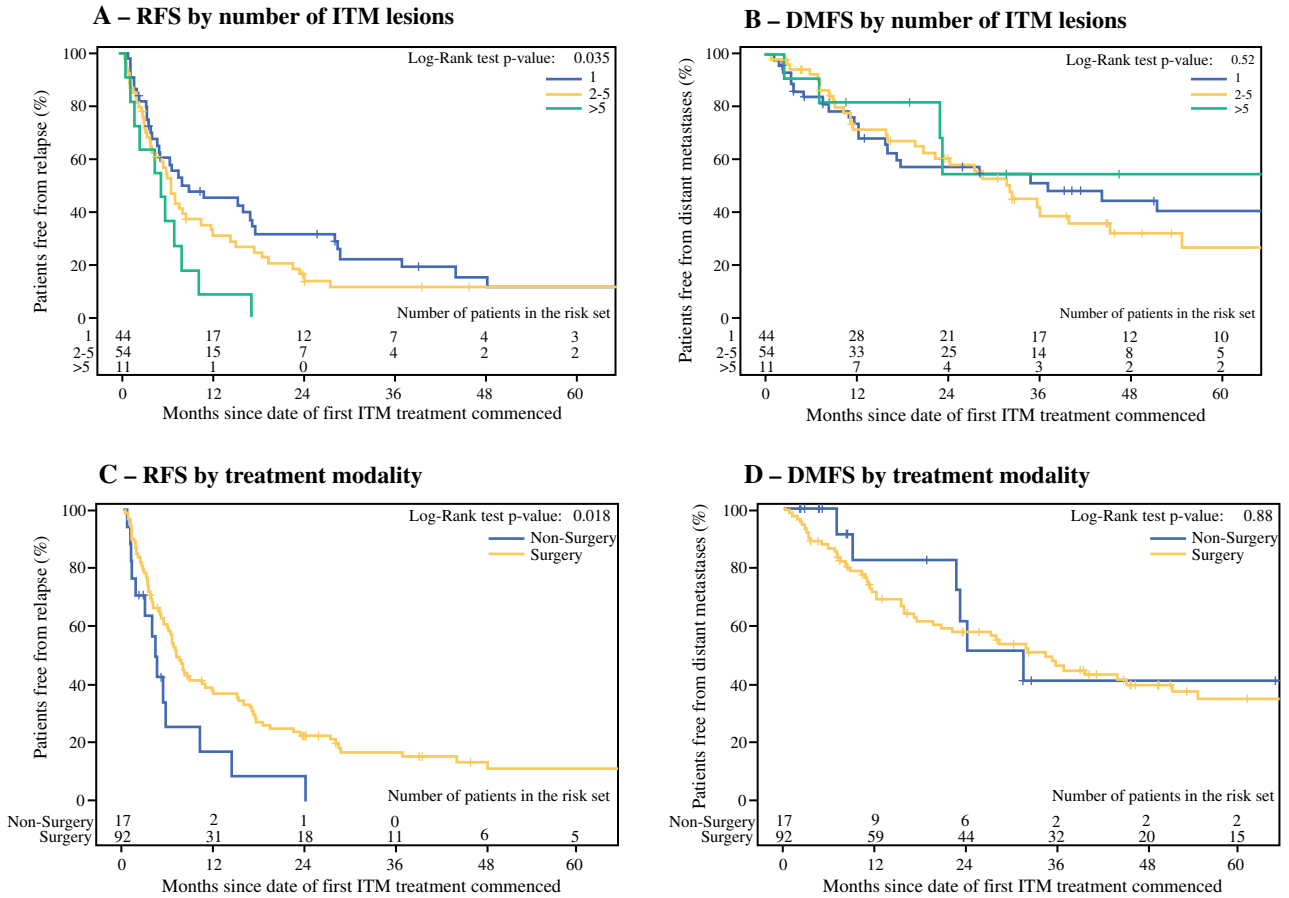

FIG. 3 Kaplan–Meier estimates of survival. Survival curves from the time of first treatment for ITM, demonstrating **a** RFS for the first ITM episode stratified by number of ITMs; **b** DMFS for patients stratified by number of ITMs in the first episode; **c** RFS for the first ITM episode stratified by treatment modality in the first episode; **d** DMFS in all patients stratified by the treatment modality used in the first episode. *ITM* in-transit metastases, *RFS* relapse-free survival, *DMFS* distant metastasis-free survival

due to the low number of patients treated with non-surgical modalities. The optimal treatment in unresectable disease, or where surgery is contraindicated, has still not been determined and should be highly individualized. Treatment modality was a predictor of RFS but did not have a significant association with DMFS or MSS. In patients with low-risk primary tumors, treatment choices should be tailored to minimize morbidity and adverse effects.

Identification of patients from a number of sources aimed to identify all patients who were treated at our center, but as the study is retrospective in nature, some eligible patients may not have been included. A further weakness of the study was the inability to fully characterize the burden of disease in terms of lesion size and if lesions were subcutaneous or dermal, due to insufficient detail in the medical records. Furthermore, the decision making regarding selection of treatment modality was difficult to define. Non-surgical options were preferred in patients with multiple lesions (particularly if present over a large area), a short disease-free interval, or where comorbidities (and anesthetic risk) favored the use of intralesional therapies.

CONCLUSIONS

This study provides an insight into the extended disease trajectory for patients with ITM, and demonstrates the current practice of surgical excision as first-line therapy in low- to moderate-burden disease. Although management when surgery is not appropriate remains highly individualized, determination of treatment modality should be based on patient, primary tumor, and ITM characteristics, and should utilize multidisciplinary expertise. Further evaluation of the role of systemic therapies is warranted. ITM characteristics were significant predictors of locoregional recurrence, but primary tumor characteristics (particularly tumor thickness, ulceration, and BRAF mutation status) were predictors of distant metastasis. This study provides longitudinal data on a large cohort of

patients with ITM, highlighting the indolent natural history that differs from most patients with advanced melanoma. Future prospective studies are required to guide clinical decision making in this patient population for whom a multitude of effective treatment strategies exist.

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