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Patterns of Failure Following Excision of In-Transit Lesions in Melanoma and Influence of Excisional Margins

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Abstract

Background and Objectives: To describe patterns of failure in patients with in-transit (IT) melanoma undergoing surgical excision.

Methods: Retrospective review of patients who underwent their first IT lesion(s) resection between May 2005 and September 2014. Cumulative incidence of local failure (new lesion within 2cm of IT resection) was estimated. Associations between clinicopathologic characteristics, local failure and any recurrence were analyzed.

Results: 130 patients presented to our institution with IT disease over the study period that met inclusion criteria. The 2-year cumulative incidence of local failure was 19.5%. Twenty-four patients developed disease within 2cm of the resected IT disease; however, only 8 were isolated local events. Cumulative incidence of local failure and of any disease differed with respect to <1 year disease-free interval (DFI) from primary melanoma to first IT event, and having >1 IT lesion at presentation. Incidence of local failure was not found to differ with respect to gross margin >5mm, after adjusting for DFI and >1 IT lesions.

Conclusions: Patients with >1 IT lesion and a DFI<1 year are at higher risk of failure after surgical excision of a first IT event. Very few failures were isolated local disease within 2cm of the IT resection scar, regardless of IT excision margin.

Keywords

Local recurrence; Disease-free interval; In-transit melanoma; Stage III; Satellites

Introduction

In-transit (IT) disease is a form of locoregional spread thought to represent tumor dissemination within dermal and subdermal lymphatics and appears as the initial site of recurrence in approximately 2–10% of patients with cutaneous melanoma. [1–4] Clinically, IT lesions manifest as cutaneous or subcutaneous tumor nodules located between the primary melanoma and the regional draining lymph node basin(s). Different nomenclature has been used to describe this disease, using distance from the primary scar to classify the disease as local recurrence, satellites or IT events. With the exception of true local recurrences secondary to residual disease after inadequate resection, these terms are arbitrary and are all considered the result of intralymphatic contamination and thus have a similarly poor prognosis. [5] In-transit disease often precedes the onset of systemic disease, with subsequent probability of survival ranging from 35 to 60% at five years. [6]

In the absence of metastatic disease, resection of IT metastases is the treatment favored when technically feasible and if the associated morbidity is acceptable. The surgical principles for treating IT lesions differ from those of a primary melanoma. The main rationale for more conservative excision of IT lesions is the concern that most patients have microscopic contamination of the draining lymphatic network, and a high likelihood of occult distant disease, recurrence and death. This is consistent with the American Joint Committee on Cancer staging system which classifies these patients as stage III. [7] Radical surgery, in order to achieve wide margins in this situation, is considered to be unjustified as this can be disfiguring and is not felt to dramatically alter the natural history of the disease, as local failure at the site of the IT lesion is not the primary concern. However, incidence rates for subsequent local disease have been reported to be as high as 45%, suggesting that local control can be an issue for some patients. In addition, previous studies have shown that a subset of IT patients, without distant metastases, enjoy long term relapse free survival following surgical resection alone with curative intent. [8–10]. Although there are no data that definitively address the gross or microscopic margin of resection in this population, the National Comprehensive Cancer Network (NCCN) recommends complete surgical excision to clear margins in the absence of extensive metastatic disease. [11]

The objective of our retrospective study was to assess patterns of failure and describe the natural history of melanoma in patients with their first IT event undergoing surgical resection at our institution, and to determine if surgical excision margins influence the risk of further local disease. This information is intended to better define how to manage patients with IT disease. By defining the patterns of failure, we intend to help address the issue if a systemic approach should be utilized at the time of first IT event secondary to the risk of distant failure or should a more aggressive local-regional approach be undertaken? This is especially relevant in an era with increasingly effective systemic therapies.

Materials and Methods

After institutional review board approval, patients 18 years of age or older who presented with IT disease as their first recurrent event and underwent surgical excision at Mayo Clinic in Rochester, MN between May 2005 and September 2014 and provided research

authorization under Minnesota state law were included in the study. Complete staging with whole body CT and/or FDG-PET scans at time of first IT event is our institutional practice, and patients with evidence of stage IV disease were excluded from this study. In-transit disease was defined broadly as any melanoma lesion in the skin or subcutaneous tissue between the primary melanoma and regional nodal basin regardless of distance. Cases consistent with a true local recurrence in the primary scar secondary to inadequate primary resection based on NCCN guidelines were excluded (n=7). Patients were also excluded if they did not have all gross disease resected (i.e., resection combined with intralesional or topical therapy for synchronous IT lesions) or the histopathologic IT excision margins were positive (n=4). Patients who presented with clinical evidence of synchronous regional nodal disease at the time of IT recurrence are at a higher risk of distant metastasis based on previous published data from our institution and were therefore excluded (n=20). [12] All clinically node negative patients were included regardless if they did or did not undergo a sentinel lymph node biopsy at the time of their IT resection and regardless of the sentinel lymph node status, if performed. Our experience with regional lymph node staging in this population has previously been described [12].

Patients with IT disease were identified using the Advanced Cohort Explorer (ACE), an advanced query tool that allows authorized users to access clinical and administrative data from multiple clinical and hospital source systems within Mayo Clinic Rochester. The search strategy included using melanoma ICD-9 codes in combination with keywords such as local recurrence/disease, IT recurrence/disease, and subcutaneous metastasis. In addition, we used the Mayo Clinic Cancer Registry and known cases of IT from physicians' personal databases to cross reference with our search results to confirm capture of all relevant cases. Using the most comprehensive search strategy, a list of 2,680 patients was generated and each electronic medical record was individually reviewed for eligibility and the reason for exclusion was recorded. In total, 250 patients were identified to have at least one IT lesion treated at our institution during our study period.

Data collected for all patients included demographic characteristics, location on the body (head and neck, trunk or extremity), primary tumor characteristics and lymph node features. We also recorded adjuvant therapy, if any, the patient received including radiation and systemic therapy (GM-CSF, vaccines, etc). At the time of each IT intervention we recorded location, number of IT lesions, diameter of the largest IT lesion, and disease-free interval from initial operation until development of IT disease. The 12 patients with synchronous IT disease at the time of their primary melanoma were assigned a DFI of 0. Detailed information about each intervention for IT metastasis was documented. All of the collected information was recorded using the secure web-based application REDCap (Research Electronic Data Capture). Only patients managed with surgical excision for their first IT event were included in this study.

Gross clinical margins around the IT lesion at the time of excision were extracted from the operative note. When more than one IT lesion was present, the margin width of the lesion with the closest clinical margin was recorded. Histopathologic margins were assessed using an ocular micrometer, and extracted from the pathology report when available. For specimens that contained no residual tumor, the gross margin was defined as the closest

peripheral margin reported using half the size of the shortest dimension of the gross specimen plus 20%. Twenty percent gross specimen shrinkage was chosen, based on data from previous studies, to translate in vitro (pathologic) to in vivo excision margin. [13]

Local failure was defined as a biopsy confirmed melanoma lesion within 2cm of the surgical scar following excision of IT disease. Thus, lesions historically referred to as satellite nodules were included in our definition of local disease failure. This definition was chosen given failure within 2cm was the widest margin we felt could be influenced by a more aggressive IT resection. Disease more than 2cm from the IT lesion, but not beyond the regional nodal basin, was defined as an IT event.

Statistical Analysis

Descriptive statistics were reported as numbers (percent) for discrete variables and as median (interquartile range) for continuous variables. Time to local failure was defined as the time from first IT diagnosis to diagnosis of local disease where regional or distant recurrence and death without local failure, or regional or distant recurrence were considered competing risk events. Time to a disease event after first IT diagnosis was defined as the time from first IT diagnosis to diagnosis of the first disease event, local, regional, or distant recurrence where death without recurrence was considered a competing risk event. The cumulative incidence functions, for the probability of local failure over time and for the probability of any recurrence over time were determined. Gray's test was used to assess whether time to local failure or time to any recurrence differed with respect to sex, age at IT diagnosis, time from primary to IT diagnosis, location, number of lesions, size of the largest lesion, gross margin width, and microscopic nodal status. Multivariate analysis was performed using competing risk analysis techniques. Model building incorporated the SCORE selection approach. A two-sided p-value less than 0.05 was considered significant. All analyses were done using SAS 9.4 computer software.

Results

Patient Characteristics

A total of 250 patients presented to our institution with IT disease over the study period. Patients were excluded due to non-surgical treatment of their first IT event (n=78), surgery performed at another institution (n=15), evidence of clinical regional nodal disease at IT presentation (n= 20) or positive surgical margins (n=7). The study cohort consists of 130 patients (53% male) where 12 (9%) patients presented with synchronous IT metastatic disease and an intact primary melanoma. Fifty-three (41%) patients presented with a first IT event within one year of their primary diagnosis, and 65 (50%) presented with their first IT event one year or more after their primary diagnosis. The median age at IT presentation was 62.8 years (IQR 53.8–74.2). (Table I). Thirty patients had dermal lesions, 87 patients had subcutaneous lesions, and 13 patients had a combination of both.

The distribution of head and neck, truncal and extremity involvement was 39%, 20% and 41%, respectively. A single IT lesion was present in 99 patients (76%), while 31 patients (24%) presented with multiple lesions. The median diameter of the largest IT lesion was

8mm (IQR, 5–15). There were 18 clinically node negative patients who underwent elective lymph node dissection or sentinel lymph node biopsy and were found to have pathologically positive nodes. The remaining 112 patients (86%) either had histologically negative lymph nodes (78 patients), or were clinically negative and did not undergo surgical/pathologic nodal staging (34 patients). Adjuvant systemic therapy was administered to 51 patients after surgical excision of their first IT event. The overwhelming majority received Leukine (GM-CSF) and additional 2 patients received interferon, a vaccine on trial or Temozolomide. Twenty one patients received adjuvant radiation. Details on both systemic and radiation adjuvant therapies can be found on Supplementary Table I.

Gross surgical margins were documented in 117 (90%) of the 130 patients, ranging from 0.5 to 50mm. The distribution of gross margins in this cohort can be seen on Supplementary Figure 1.

Patterns of Failure

When the data was locked, the 44 patients who were alive without a disease recurrence had been followed a median of 2.8 years from their first IT event. Among the 81 recurrences observed, there were few instances where the site(s) of failure after first in-transit event was an isolated local failure (8 pts.; 6%). A local failure was found more often in combination with another failure site (15 pts; 11.5%). However, more than half of the failures observed were recurrences without local failure (58 pts.; 44.6%) (Table II).

Forty-seven patients died during our study time period: 37 died with disease progression, 7 died without evidence of disease, and 3 died with unknown disease status.

Local Failure

The overall cumulative local failure was 19.5% (95% CI: 11.9–26.4%) at 2 years after IT surgery. Local events occurred in the previous IT scar or surgical bed of 11 patients, and within 2 cm of the IT surgical scar in 12 patients. Univariate analysis found that the incidence of local failure differed with respect to whether DFI was less than one year ($p=0.048$), if more than one lesion was present ($p=0.004$) and gross margin $> 5\text{mm}$ ($p=0.06$). The 2-year cumulative incidence of local failure was 31.6% (95% CI: 15.5–44.5%) for margins of 5mm or less and 13.3% (95% CI: 6.0–20.3%) for margins over 5mm. The 2-year cumulative incidence of local failure for patients with DFI ≤ 1 year was 27.3% (95% CI: 13.9–38.6%) and 14.3% (95% CI: 4.5–23.0%) in those with DFI of over a year. The 2-year cumulative incidence of local failure for patients with more than one IT lesion at the time of first IT event was 40.3% (95% CI: 17.7–56.7%) and 13.4% (95% CI: 4.8–21.0%) in those with a single lesion. The cumulative probability of local failure for patients with and without these high risk characteristics are shown in Figure 1. No significant associations were found between incidence of local failure and age greater than 65 years old at first IT event ($p=0.92$), sex ($p=0.29$), location of the primary (extremities vs. trunk: $p=0.26$; head & neck vs. trunk: $p=0.13$) or diameter of the largest IT lesion greater than or equal to 10 mm ($p=0.35$) (Table III).

Multivariate analysis found higher local failure rates in patients with a DFI of less than one year (HR=2.66; 95% CI: 1.10–6.40; $p=0.03$) and more than a single IT lesion at presentation

(HR=4.48; 95% CI: 1.94–10.33; $p < 0.01$) was also seen on multivariate analysis (Table IV). After accounting for DFI < 1 year or more than 1 IT lesion being present, the cumulative probability of local failure was not found to differ with respect to gross margins > 5 mm ($p=0.358$).

Cumulative Incidence of any Recurrence – local, regional or distant

The overall cumulative incidence of any recurrence was 71.3% (95% CI: 60.3–79.3) at 2 years after IT resection. Univariate analysis found that the incidence of any failure differed with respect to whether DFI was less than one year ($p=0.03$) and if more than one lesion was present ($p=0.014$). (Table III). The 2-year cumulative incidence of any failure for patients with DFI < 1 year was 75.2% (95% CI: 58.5–85.2%) and 71.3% (95% CI: 54.5–81.9%) in those with DFI over a year. The 2-year cumulative incidence of any failure for patients with more than one IT lesion at the time of first IT event was 82.3% (95% CI: 56.7–92.7%) and 67.5% (95% CI: 54.3–76.9%) in those with a single lesion. No significant associations were found between incidence of any recurrence and age greater than 65 years old at first IT event ($p=0.08$), sex ($p=0.31$), location of the primary (head & neck vs. trunk: $p=0.09$); diameter of the largest IT lesion greater than or equal to 10 mm ($p=0.17$) or gross margin > 5 mm ($p=0.33$).

Multivariate analysis found that higher failure rates were associated with less than one year DFI (HR=1.70; 95% CI: 1.10–2.6; $p=0.02$) and more than a single IT lesion (HR=2.4; 95% CI: 1.5–3.7; $p < 0.01$) (Table IV).

Discussion

Our study supports the premise that the onset of IT disease is associated with a poor prognosis and often precedes the development of systemic metastasis. Moreover, isolated local failure following surgical excision of an IT lesion is uncommon. The 2-year cumulative event rate within 2cm of a previous IT resection was 19.5%; however, the majority of these were not isolated but were associated with other recurrences (IT, regional or distant). The 2-year cumulative recurrence rate after resection of a first IT event was 71.3%. The factors associated with a higher incidence of any recurrence were more than one IT lesion at first IT event and a short DFI between primary diagnosis and first IT event.

Wider gross margins (> 5 mm) of resection of IT lesions were associated with $\frac{1}{2}$ as many failures within 2cm of IT resection scar; however, this did not reach statistical significance nor did gross margin width impact incidence of any recurrence. Having more than one IT lesion and DFI less than 1 year, were the only factors associated with local failure (within 2cm of the IT resection scar). Similar to the published literature, our population of patients with IT melanoma have a high propensity to develop subsequent locoregional failures following surgical excision. Approximately, 44% (51 of 130) of our cohort developed a locoregional recurrence after achieving negative microscopic margins of resection of their IT disease but only 8 of these recurrences manifested as local failure alone. Based on these findings our approach for excision of IT lesions is ideally to obtain 5mm gross margins if primary closure can be obtained with minimal potential morbidity and if not, then resection to the most minimal margin that would obtain negative microscopic margins.

The rationale for excising primary melanoma with 1 to 2 cm margins is to remove microsatellites in the field that could otherwise persist and later cause local failure. Evidence based guidelines, supported by randomized control trials, define the gross clinical margins that should be excised around the primary lesion at the time of definitive resection is directed by the tumor thickness. Unfortunately, no evidence based guidelines exist for the width of excision around IT lesions. For IT disease, the goal of resection is to remove the measureable disease, accepting a risk of lymphatic contamination and recurrence beyond what is clinically evident. Thus, a philosophy that wider margins can't influence the natural history of the disease is often taken, as well as an understanding that radical surgery employing extensive margins can lead to significant morbidity. Accepting the limited data available to define the principles for resection of IT lesions, the NCCN recommends excision of the entire extent of the disease, with the goal of obtaining microscopically negative margins. [11]

The 5-year survival for patients with IT disease is poor, but there seems to be a subgroup of patients that will be cured with local excision alone. In our series, 43 patients did not recur with a median follow-up of 2.8 years. Our series spans a time period before the approval of modern immunotherapy for advanced stage III disease and thus shows the natural history following resection of a first IT event without the use of effective adjuvant systemic therapy. Approximately 1/4 of all subsequent disease events were within 2cm of the first IT resection, suggesting this could potentially have been prevented with wider margins. Of these events, only 8 patients had isolated local disease as their next event. Previous studies have looked at prognostic factors related to survival after IT disease, none to our knowledge, have specifically addressed the influence of gross margins on the natural history of the disease. [11]

Adequate local control obtained at this first recurrent event could be the first step in identifying a subset of patients with more favorable tumor biology; hence, better prognosis and potentially cured with conservative excision alone. Until genetic profiling and/or molecular markers of the lesions are identified which predict their natural behavior, surgical excision, +/- sentinel lymph node biopsy, may be a reasonable approach to avoid adjuvant therapies in patients presenting with single, node negative first IT events. The ideal approach can certainly be debated, as in our series 34% (44/130) of patients were free of recurrence with a median follow-up of 2.8 years following excision alone. Approximately 44% of subsequent events were further local-regional failures, which remain potentially salvageable, yet ultimate distant recurrence remains fairly high and our DFS was only 28.7%. Our prior work also suggests patients with IT recurrence can be stratified into high, intermediate and low risk groups based on nodal status; macroscopic, microscopic (sentinel lymph node biopsy positive) and pathologically node negative disease, respectively. [12]

There is great variability in reported survival outcomes for patients with Stage III disease. This holds true when limited to IT metastasis only, secondary to the heterogeneity of the disease as well as differencing inclusion criteria and outcomes being reported. Dong et al published on a cohort of 648 patients with cutaneous melanoma who experienced local recurrence (recurrence within 5cm of the primary without nodal or systemic recurrent disease) as their first disease event. [8] Fifty-six percent of their patients had local

recurrences within 2 years of their primary diagnosis. In spite of differences in methodologies and inclusion/exclusion criteria, such as ours including those with microscopic nodal disease and IT events beyond 5cm, our results are consistent with their findings. They reported 196 (30%) patients developed another local recurrence following resection of an intralymphatic lesion within 5cm of the original primary melanoma resection scar, 178 (27%) developed IT disease, and 150 (23%) experienced distant recurrences. The remaining 20% had no further progression. Similar to our study they also reported that shorter DFI was associated with worse outcomes.

We have made every attempt to make our study group as homogenous as possible; despite this our study has several limitations. Patients with IT metastasis vary greatly in terms of number, depth, location and distribution of lesions. They also present with diverse patterns of failure and frequently experience multiple treatment modalities. We attempted to minimize this by only including patients who had their first IT event and all gross disease resected with negative microscopic margins at our institution. As a result the outcome of these patients is likely more favorable than an unselected group of patients with IT disease who may have numerous lesions and unresectable disease requiring alternative therapies. This was not a randomized trial but a retrospective review and bias was evident in the preferred margin of excision by the surgeons. Another limitation was almost 1/3 of the patients did not have histologic margin width specified in their pathology report, prohibiting us from any detailed analysis utilizing this variable.

Local, satellite and IT metastases are all part of the same disease spectrum that is distinguished arbitrarily by distance from the primary resection scar. We specifically chose to look at the association margin width could have on the development of disease within 2 cm of the resected IT lesion because this appears to have the most clinical practicality. Ultimately, disease developing so close to the previous IT site is an outcome the surgeon could potentially prevent by performing wider surgical margins. As a result of our goal we grouped all events within 2 cm of the IT resection together, thus including some that historically would have been referred to as satellites.

Conclusion

In conclusion, for patients presenting with a first IT event that is resectable, we found both the incidence of local failure and the incidence of any recurrence was increased in patients with more than one IT lesion and a DFI between primary diagnosis and IT event of less than one year. We did not find a significant difference in either the incidence of local failure or any recurrence among those with a gross margin $>$ or $\leq$ 5mm. This report is the largest experience evaluating the association of margin width and further recurrence in the setting of resection of first IT event. We found that clinical margin of $>$ 5mm is associated with a nonsignificant trend for lower risk of another event within 2 cm of previously resected IT lesion; however, wider margins offered no additional benefit in DFS and very few patients presented with isolated local disease within 2 cm of the IT resection scar. Based on our findings a 5mm gross margin and no tumor on ink as a microscopic margin should be attempted when resecting a first isolated IT lesion, if this can be accomplished with primary closure. Narrower clinical margins of resection are acceptable and should be made on a case

by case basis to decrease morbidity since isolated local failure near the IT excision is rarely a concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis:

A retrospective review of first time in-transit events suggests that a clinical margin of >5mm is not associated with a lower risk of failure within 2cm. Disease-free interval less than 1 year and multiple IT lesions confer a higher risk. The majority of patients fail beyond this resected IT site.

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FIGURE 1:
Estimated Cumulative Incidence of Local Failure after Surgical Excision of First In-transit Event by Number of IT Lesions (a) and by Disease-Free Interval (b).

TABLE I.

Clinicopathologic Characteristics of Patients Undergoing Surgical Excision for a First In-Transit Recurrence.

Variable	N=130
Age in years, median (IQR)	62.8 (53.8-74.2)
Male, n (%)	69 (53)
Disease free interval in months, n (%)	
1 year	53 (41)
>1 year	65 (50)
Synchronous IT disease at primary melanoma diagnosis	12 (9)
Location, n (%)	
Head & Neck	51 (39)
Trunk	26 (20)
Extremities	53 (41)
Number of IT lesions, n (%)	
=1	99 (76)
>1	31 (24)
Diameter of largest IT lesion in mm, median (IQR)	8 (5-15)
Diameter of largest IT lesion, n (%)	
<10mm	64 (49)
10mm	57 (44)
Unknown	9 (7)
Synchronous microscopic nodal disease, n (%)	18 (14)
Gross margin of IT excision in mm, median (IQR)	11.2 (5-15)
Gross margin of IT excision, n (%)	
5mm	47 (36)
>5mm	70 (54)
Unknown	13 (10)
Adjuvant radiation therapy, n (%)	21 (16)
Adjuvant systemic therapy, n (%)	51 (39)

IT, in transit; IQR, interquartile range.

TABLE II.

Recurrence Patterns after Surgical Resection of a First In-Transit Event

Type of Recurrence	n=130
No Recurrence	49 [*] (37.7%)
Local Metastases only	8 (6.2%)
Local + In Transit Metastases	12 (9.2%)
Local + Regional Metastases	1 (0.8%)
Local + Distant Metastases	1 (0.8%)
Local + In Transit + Distant Metastases	1 (0.8%)
In Transit Metastases only	21 (16.2%)
Regional Metastases only	6 (4.6%)
Distant Metastases only	20 (15.4%)
In Transit + Regional Metastases	3 (2.3%)
Regional + Distant Metastases	6 (4.6%)
In Transit + Regional + Distant Metastases	2 (1.5%)

* Five patients died without documentation of disease recurrence

Estimated Cumulative Incidence of Local Recurrence and Any Recurrence after Surgical Excision of First In-Transit Event

TABLE III.

	N	Local Recurrence			Any Recurrence		
		2-Year Cumulative Incidence (95% CI)	Hazard Ratio (95% CI)	p-value	2-Year Cumulative Incidence (95% CI)	Hazard Ratio (95% CI)	p-value
Total Population	130	19.5%(11.9-26.4)	--	--	71.3%(60.3-79.3)	--	--
Sex							
Male	69	24.8%(12.8-35.1)	1.6 (0.7-3.8)	0.29	82.3%(60.7-92.0)	1.3 (0.8--3.0)	0.31
Female	61	13.8%(4.4-22.3)	1.0		63.2%(46.6-74.6)	1.0	
Age at first IT event							
65 years	60	19.6%(8.4-29.4)	1.04 (0.5-2.4)	0.92	63.1%(45.4-275.1)	0.7 (0.4-1.1)	0.08
<65 years	70	19.4%(8.7-28.9)	1.0		79.1%(63.1-88.2)	1.0	
Disease free interval							
1 year	53	27.3%(13.9-38.6)	2.4 (1.01-5.5)	0.048	75.2%(58.5-85.2)	1.6 (1.0-2.6)	0.03
>1 year	65	14.3%(4.5-23.0)	1.0		71.3%(54.5-81.9)	1.0	
Synchronous IT mets	12	----	----		----	----	
Location							
Extremities	53	18.3%(6.7-28.4)	2.5 (0.5-12.0)	0.26	60.2%(42.2-72.6)	0.5 (0.3-0.95)	0.03
Head & Neck	51	27.6%(12.5-40.1)	3.3 (0.7-15.5)	0.13	77.6%(55.9-88.6)	0.6 (0.3-1.1)	0.09
Trunk	26	7.7%(0.0-17.4)	1.0		83.3%(57.2-93.5)	1.0	
Gross Margin							
5mm	47	31.6%(15.5-44.5)	2.3 (0.98-5.3)	0.06	75.5%(51.5-87.6)	1.3 (0.8-2.0)	0.33
>5mm	70	13.3%(4.8-21.0)	1.0		68.0%(52.0-78.7)	1.0	
Unknown	13	---	---		---	---	
Number of IT lesions							
>1	31	40.3%(17.7-56.7)	3.3 (1.5-7.5)	0.004	82.3%(56.7-92.7)	1.8(1.1-3.0)	0.014
=1	99	13.4%(6.0-20.3)	1.0		67.5%(54.3-76.9)	1.0	

	N	Local Recurrence				Any Recurrence			
		2-Year Cumulative Incidence (95% CI)	Hazard Ratio (95% CI)	p-value	2-Year Cumulative Incidence (95% CI)	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Diameter of largest IT lesion	57	14.8% (4.8-23.7)	0.7 (0.3-1.6)		70.6% (54.5-81.0)	1.4 (0.9-2.2)			
	64	23.6% (11.8-33.8)	1.0	0.35	74.0% (56.3-84.6)	1.0			0.17
	9	---	---		---	---			
Synchronous nodal disease	18	23.2% (0.3-40.7)	1.2 (0.4-3.4)	0.71	74.1% (41.7-88.5)	1.1 (0.6-2.0)			0.67
	112	18.6% (10.6-25.9)	1.0		71.2% (58.6-80.0)	1.0			

TABLE IV.

Multivariate Analysis of Factors Associated with Local Recurrence or Any Recurrence.

Variable	Local Recurrence		Any Recurrence	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Disease free interval *				
1 year	2.66 (1.10-6.40)	0.03	1.7 (1.1-2.6)	0.02
>1 year	1.0		1.0	
Number of IT lesions				
>1	4.48 (1.94-10.33)	<0.01	2.4 (1.5-3.7)	< 0.01
=1	1.0		1.0	

CI, confidence intervals; IT, in transit.

* A total of 12 patients with synchronous IT disease are excluded from these analyses.