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Stage-specific disease recurrence and survival in localized and regionally advanced cutaneous melanoma

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ABSTRACT

Objective: To investigate stage-specific survival from diagnosis, stage-specific disease recurrence, and post-recurrence survival in patients diagnosed with localized and regionally advanced cutaneous melanoma.

Methods: A retrospective, observational cohort study was conducted in six Dutch hospitals. We included patients with a first diagnosis of stage I, II, or III melanoma between January 2003 and December 2011. Descriptive statistics were used to summarize time to first recurrence and type of first recurrence. Overall survival (OS) from diagnosis and post-recurrence OS were assessed using the Kaplan-Meier method.

Results: A total of 3,093 patients had a first diagnosis of stage I ($n = 2,299$), II ($n = 565$), or III ($n = 229$) melanoma. Median OS was not yet reached for patients with stage I, 9.5 years for patients with stage II, and 6.8 years for patients with stage III. Fifty-seven patients (8%) with stage IB, 137 patients (29%) with stage II, and 81 patients (47%) with stage III developed disease recurrence. Median time to first recurrence was 2.8, 1.5, and 1.0 years for patients with stage IB, II, and III, respectively. Most patients (79%) developed regional lymph node or distant metastases as first recurrence. Median post-recurrence OS was 2.8, 3.9, and 0.5 years for patients with intralymphatic, regional lymph node, and distant metastases, respectively.

Conclusion: A substantial number of patients developed disease recurrence. Of these patients, a considerably high proportion developed distant metastases which had a great impact on survival. Identifying disease recurrence at its earliest stage is crucial because metastatic melanoma remains incurable for most patients.

Introduction

Cutaneous melanoma is one of the most common cancers in Europe, with more than 100,000 new cases each year [1]. The majority of patients (more than 80%) are diagnosed with localized melanoma (i.e., American Joint Committee on Cancer [AJCC] stage I and II) and have a rather favorable prognosis [2,3]. European five-year survival rates range from 95% to 100% for patients with stage I and from 65% to 93% for patients with stage II [4].

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In general, patients with localized melanoma can be cured by surgical excision of the primary tumor. More than ten percent of these patients will, however, develop disease recurrence. The rate of recurrence is even higher (more than 50%) in patients with regionally advanced melanoma (i.e., AJCC stage III) [5–15]. As a consequence of disease recurrence, approximately 20% of patients will eventually develop metastatic disease (i.e., AJCC stage IV) [2]. Despite recent development of novel immunotherapeutic and targeted drugs, metastatic melanoma remains incurable for most patients [16]. The European five-year survival rate ranges from 9% to 28% [4].

Disease recurrence in localized and regionally advanced melanoma have been previously discussed in the literature [5–15]. Most studies were, however, limited to patients with disease recurrence [7,10,12–14] and/or did not report stage-specific disease recurrence [5–8,11–14]. Such knowledge is, however, essential for assessing the risk of disease recurrence at the moment of diagnosis. Furthermore, some studies did not report post-recurrence survival [6,7,14,15], which is vital for providing insight into the impact of disease recurrence on survival. Therefore, the aim of this study was to investigate stage-specific survival from diagnosis, stage-specific disease recurrence, and post-recurrence survival in patients diagnosed with localized and regionally advanced cutaneous melanoma.

Methods

Study population

We conducted an observational cohort study in six Dutch hospitals (four general and two academic). Patients were identified using data from the nationwide Netherlands Cancer Registry (NCR). We included all patients with a first diagnosis of AJCC stage I, II, or III cutaneous melanoma between January 2003 and December 2011.

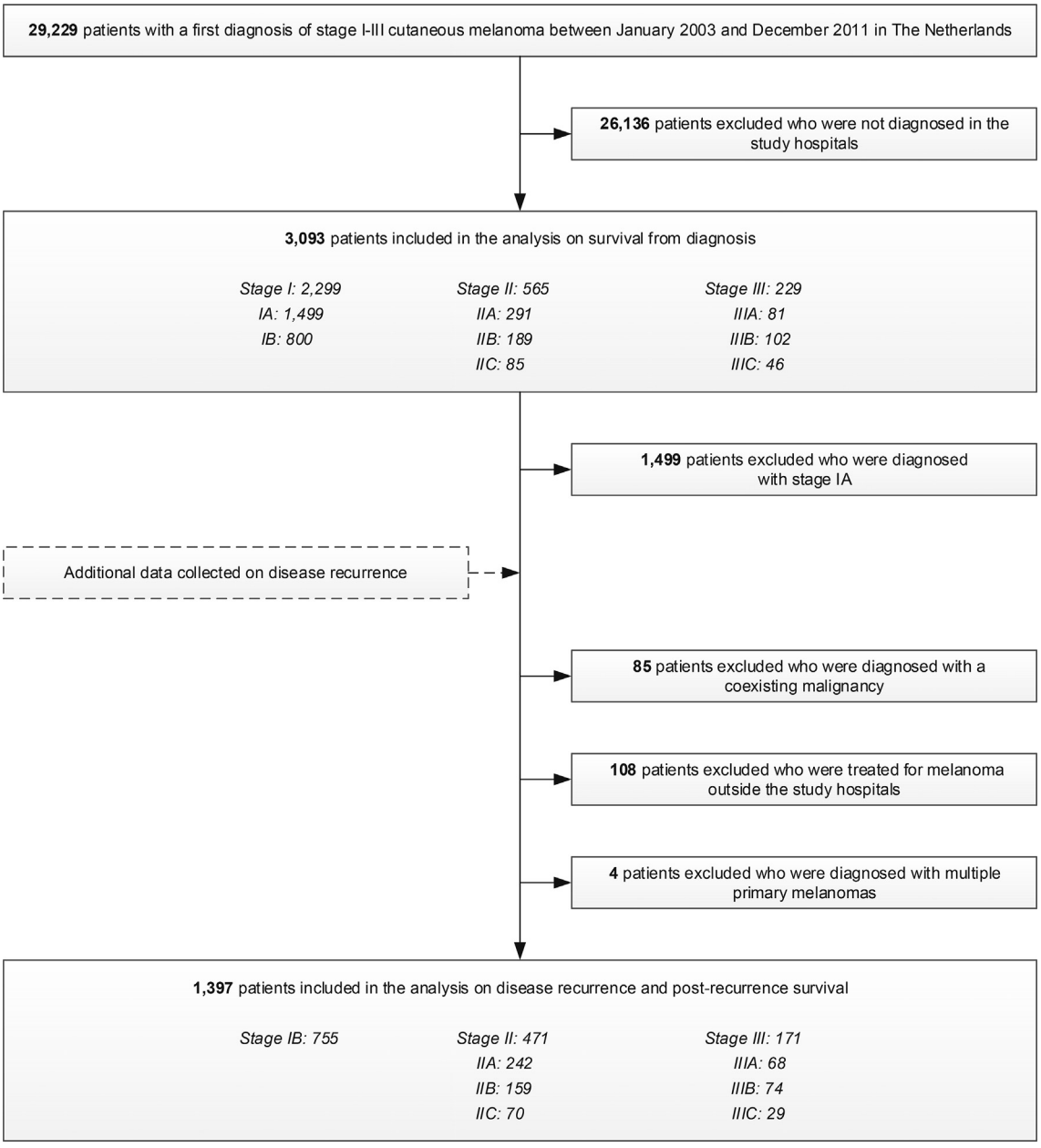

Fig. 1. Patient flowchart.

Data collection

Data were retrospectively collected using a two-pronged approach. First, we retrieved two datasets from the NCR (data cut-off: April 2014): one for the entire Dutch melanoma population and one for the population in the study hospitals. Both datasets contained identical data (baseline patient and tumor characteristics, and survival) and were used to assess the representativeness of the population in the study hospitals for the Dutch melanoma population. Secondly, we collected additional data on disease recurrence for all patients diagnosed with stage IB to III in the study hospitals using hospital medical records. No additional data were collected for patients diagnosed with stage IA because we assumed that disease recurrence would not be related to survival in these patients. Furthermore, no additional data were collected for patients who were diagnosed with a coexisting malignancy in the past five years (exceptions: basal cell carcinoma and squamous cell carcinoma of the skin), who were treated for melanoma outside the study hospitals, and/or who were diagnosed with multiple primary melanomas. Data collection was completed in December 2015. The medical research ethical committees exempted the study from informed consent because the study was not subject to the Medical Research Involving Human Subjects Act.

Statistical analysis

All patients were grouped according to their stage at diagnosis: I, II, or III. Baseline characteristics were summarized using descriptive statistics. Continuous variables were depicted as medians and interquartile ranges (IQR), and categorical variables as counts and proportions. Differences in proportions between the patient groups were analyzed using the two-tailed chi-squared test. The Kruskal-Wallis test was used to compare medians.

For all patients, follow-up, overall survival (OS), and survival rates were calculated from the date of diagnosis until the date of death or last follow-up using the Kaplan-Meier method. Survival curves were presented by stage and substage. For patients with stage IB to III, time to first event (i.e., disease recurrence or death) was also assessed using the Kaplan-Meier method. In this analysis, survival time was calculated from the date of diagnosis until the date of first recurrence, death, or last follow-up. The cumulative incidence of the first event was assessed according to the cumulative incidence competing risk method. For patients with disease recurrence, we evaluated the type of first recurrence, time to first recurrence, presence of distant metastases (either as first or subsequent recurrence), and post-recurrence survival. The type of first recurrence was classified as local recurrence, intralymphatic metastasis (either satellite or in-transit metastasis), regional lymph node metastasis, or distant metastasis and categorized by the most advanced recurrence (e.g., distant metastases outranked regional lymph node metastases). Time to first recurrence was calculated from the date of diagnosis until the date of first recurrence. Post-recurrence survival (OS and survival rates) was assessed according to the Kaplan-Meier method and calculated from the date of first recurrence until the date of death or last follow-up. Post-recurrence survival curves were presented by stage at initial diagnosis and type of first recurrence.

All analyses were conducted using STATA statistical analysis software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Study population

A total of 3,093 patients had a first diagnosis of stage I ($n = 2,299$; 74%), II ($n = 565$; 18%), or III ($n = 229$; 7%) cutaneous melanoma in the six study hospitals (Fig. 1). Almost half of the patients ($n = 1,499$; 48%) was diagnosed with stage IA. Of the patients with stage IB to III ($n = 1,594$; 52%), we excluded 197 patients: 85 patients were diagnosed with a coexisting malignancy in the past five years, 108 patients were treated for melanoma outside the study hospitals, and four patients were diagnosed with multiple primary melanomas. The remaining 1,397 patients consisted of 755 patients (54%) with stage IB, 471 patients (34%) with stage II, and 171 patients (12%) with stage III.

The baseline patient and tumor characteristics of the Dutch melanoma population and the population in the study hospitals were comparable (Supplemental Table). Table 1 presents the baseline characteristics of the population in the study hospitals. Patients with stage I were younger and more often female than patients with stage II and III. In all stages, the majority of patients was diagnosed with melanoma on the trunk or lower extremities, and superficial spreading or nodular melanoma.

Stage-specific survival from diagnosis

Fig. 2 shows the Kaplan-Meier curves for OS from diagnosis. At a median follow-up of 5.4 years, median OS was not yet reached for patients with stage I, 9.5 years (95% confidence interval [CI]: 7.9-not reached [NR]) for patients with stage II, and 6.8 years (95% CI: 5.3-NR) for patients with stage III. Five-year survival rates were 94%, 66%, and 59% for patients with stage I, II, and III, respectively. Within substages of stage I, the five-year survival rate was somewhat higher for patients with stage IA (95%) than for patients with stage IB (91%). Median OS within substages of stage II was longer for patients with stage IIA (10.5 years; 95% CI: 9.3-NR) than for patients with stage IIB (8.5 years; 95% CI: 5.8-NR) and IIC (4.5 years; 95% CI: 3.1-6.6). The five-year survival rate ranged from 74% for patients with stage IIA to 46% for patients with stage IIC. Within substages of

Table 1
Baseline characteristics.

	Stage I	Stage II	Stage III
	n=2,299	*n=565*	*n=229*
Age, *yrs*			
Median (IQR)	54 (43–64)	63 (50–74)	58 (45–69)
Gender, *n (%)*			
Male	915 (40%)	286 (51%)	138 (60%)
Female	1,384 (60%)	279 (49%)	91 (40%)
Topography, *n (%)*			
Head and neck	267 (12%)	85 (15%)	27 (12%)
Trunk	925 (40%)	187 (33%)	99 (43%)
Upper extremity	484 (21%)	130 (23%)	27 (12%)
Lower extremity	619 (27%)	162 (29%)	74 (32%)
Unknown	4 (0%)	1 (0%)	2 (1%)
Morphology, *n (%)*			
Superficial spreading	1,846 (80%)	216 (38%)	106 (46%)
Nodular	83 (4%)	207 (37%)	74 (32%)
Lentigo maligna	96 (4%)	6 (1%)	0 (0%)
Acral lentiginous	10 (0%)	10 (2%)	2 (1%)
Other	38 (2%)	39 (7%)	9 (4%)
Unknown	226 (10%)	87 (15%)	38 (17%)
Tumor thickness, *mm, n (%)*			
≤ 1.00	1,662 (72%)	0 (0%)	14 (6%)
1.01–2.00	608 (26%)	73 (13%)	53 (23%)
2.01–4.00	0 (0%)	307 (54%)	85 (37%)
> 4.00	0 (0%)	180 (32%)	68 (30%)
Unknown	29 (1%)	5 (1%)	9 (4%)
Ulceration, *n (%)*			
No	2,098 (91%)	312 (55%)	131 (57%)
Yes	200 (9%)	252 (45%)	86 (38%)
Unknown	1 (0%)	1 (0%)	12 (5%)

IQR: interquartile range; mm: millimeter; *n*: number; yrs: years.

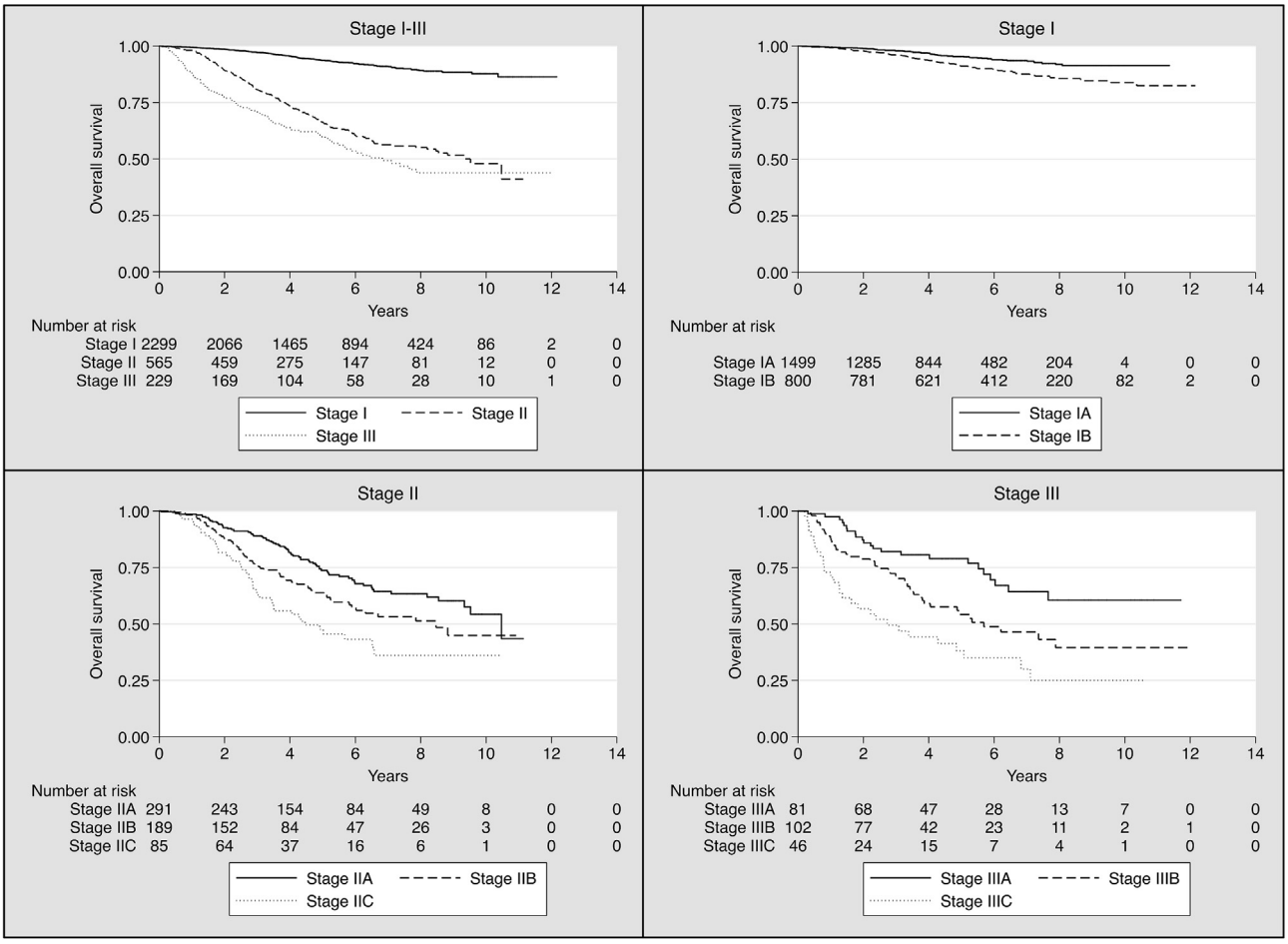

Fig. 2. Kaplan-Meier curves for overall survival from diagnosis.

stage III, median OS was not yet reached for patients with stage IIIA, 5.7 years (95% CI: 3.8-NR) for patients with stage IIIB, and 2.7 years (95% CI: 1.3–5.1) for patients with stage IIIC. The five-year survival rate was 77%, 52%, and 35% for patients with stage IIIA, IIIB, and IIIC, respectively.

Stage-specific disease recurrence

Fig. 3 shows the Kaplan-Meier curves for the time to first event and the cumulative incidence curves of both events (i.e., disease recurrence and death). The median time to first event was not yet reached for patients with stage IB, 7.9 years (95% CI: 5.3–9.5) for patients with stage II, and 3.7 years (95% CI: 1.8–5.1) for patients with stage III. In all stages, the five-year cumulative incidence of disease recurrence as first event was higher than the five-year cumulative incidence of death as first event: 7% versus 4% for patients with stage IB, 30% versus 13% for patients with stage II, and 47% versus 10% for patients with stage III, respectively.

Table 2 presents the type of first recurrence, time to first recurrence, and presence of distant metastases for patients with disease recurrence. In all stages, most patients developed regional lymph node (42%, 37%, and 31% of patients with stage IB, II, and III, respectively) or distant metastases (35%, 42%, and 48%, respectively) as first recurrence. The median time to first recurrence was longer for patients with stage IB (2.8 years; 95% CI: 0.5–8.4) than for patients with stage II (1.5 years; 95% CI: 0.4–5.5) and III (1.0 years; 95% CI: 0.2–5.1). By type of first recurrence, the median time to regional lymph node and distant metastases was 3.0 and 3.1 years for patients with stage IB, 0.8 and 2.2 years for patients with stage II, and 0.5 and 1.1 years for patients with stage III, respectively. In total, approximately two-thirds of the patients with disease recurrence developed distant metastases. Distant metastases occurred more often as first recurrence than as subsequent recurrence; this difference increased with advancing disease stages.

Post-recurrence survival

Fig. 4 shows the Kaplan-Meier curves for post-recurrence OS. Median post-recurrence OS was 1.9 years (95% CI: 0.8–3.2) for patients initially diagnosed with stage IB, 1.5 years (95% CI: 1.1–2.1) for patients initially diagnosed with stage II, and 1.1 years (95% CI: 0.6–2.2) for patients initially diagnosed with stage III. Two-year post-recurrence survival rates were 41%, 42%, and 43% for patients initially diagnosed with stage IB, II, and III, respectively. By type of first recurrence, median post-recurrence OS was longer for patients with regional lymph node metastases (3.9 years; 95% CI: 2.5-NR) than for patients with intralymphatic (2.8 years; 95% CI: 1.9–4.6) and distant metastases (0.5 years; 95% CI: 0.3–0.6). The two-year post-recurrence survival rate was 57% for patients with intralymphatic metastases, 65% for patients with regional lymph node metastases, and 12% for patients with distant metastases.

Discussion

We investigated stage-specific survival from diagnosis, stage-specific disease recurrence, and post-recurrence survival in

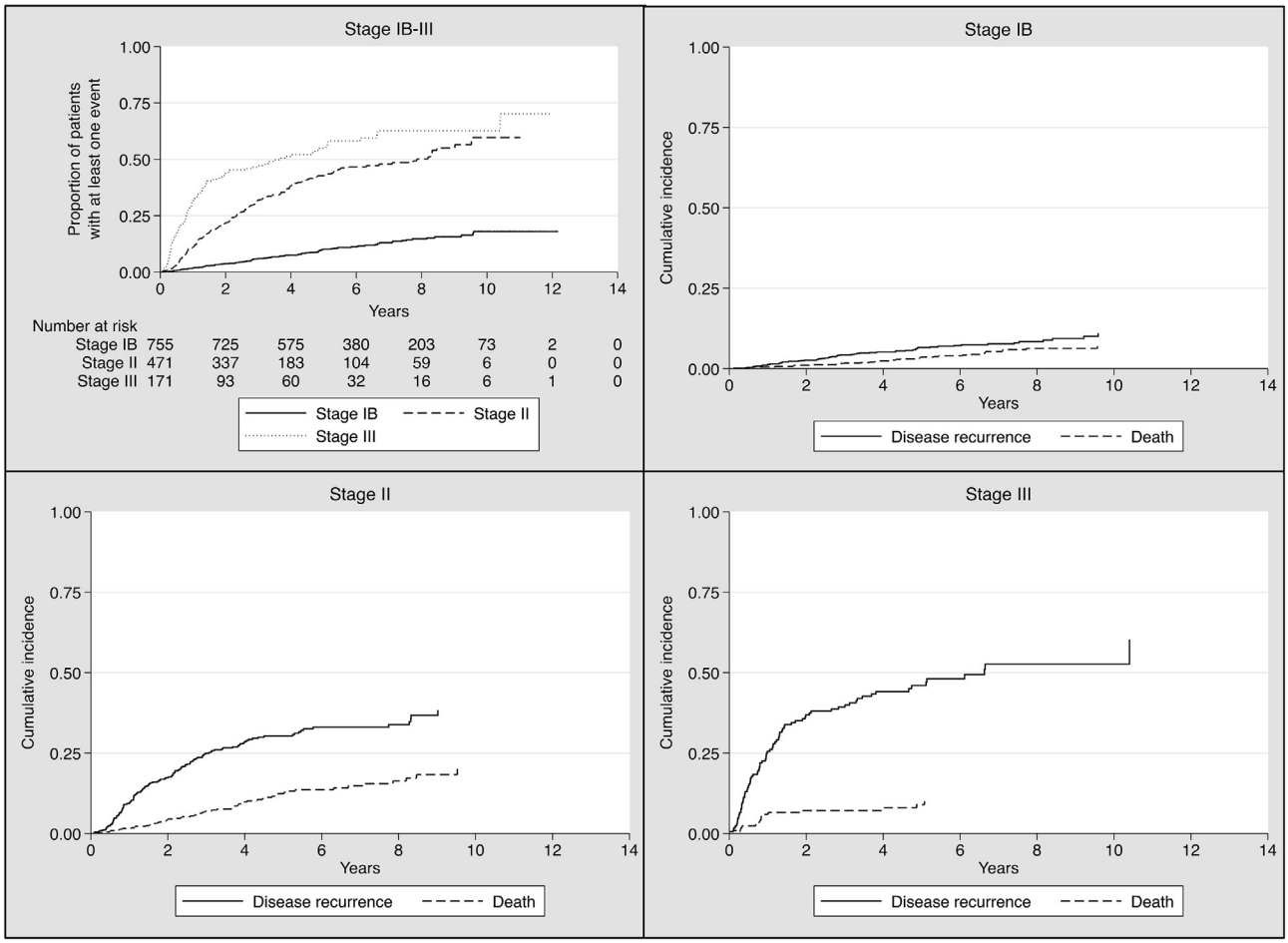

Fig. 3. Kaplan-Meier curves for the time to first event and cumulative incidence curves of both events.

Table 2
Type of first recurrence, time to first recurrence, and presence of distant metastases.

	Stage IB	Stage II	Stage III
	n=755	*n=471*	*n=171*
Recurrence status, *n (%)*			
Event-free	698 (92%)	334 (71%)	90 (53%)
Disease recurrence	57 (8%)	137 (29%)	81 (47%)
Type of first recurrence, *n (%)*			
Local recurrence	3 (5%)	4 (3%)	2 (2%)
Intralymphatic metastasis	10 (18%)	25 (18%)	15 (19%)
Regional lymph node metastasis	24 (42%)	51 (37%)	25 (31%)
Distant metastasis	20 (35%)	57 (42%)	39 (48%)
Time to first recurrence, *yrs, median (95% CI)*			
Any recurrence	2.8 (0.5–8.4)	1.5 (0.4–5.5)	1.0 (0.2–5.1)
Intralymphatic metastasis	2.1 (0.7–7.4)	2.1 (0.5–5.4)	1.3 (0.3–3.8)
Regional lymph node metastasis	3.0 (0.6–8.4)	0.8 (0.3–3.1)	0.5 (0.1–5.1)
Distant metastasis	3.1 (0.5–8.6)	2.2 (0.6–8.3)	1.1 (0.2–6.6)
Distant metastases, *n (%)*			
No	21 (37%)	46 (34%)	27 (33%)
Yes	36 (63%)	91 (66%)	54 (67%)
First recurrence	20 (56%)	57 (63%)	39 (72%)
Second recurrence or higher	16 (44%)	34 (37%)	15 (28%)

CI: confidence interval; *n*: number; yrs: years.

patients with a first diagnosis of stage I, II, or III cutaneous melanoma in six Dutch hospitals. As expected, patients with stage I had a longer OS from diagnosis (median not yet reached) than patients with stage II (9.5 years) and III (6.8 years). In line with this finding, disease recurrence occurred more often in patients with stage III (rate of recurrence: 47%) than in patients with stage I (8%) and II (29%). Most patients (79% of all patients with disease recurrence) developed regional lymph node or distant metastases as first recurrence. Post-recurrence OS stratified by stage at diagnosis was comparable. However, post-recurrence OS differed by type of first

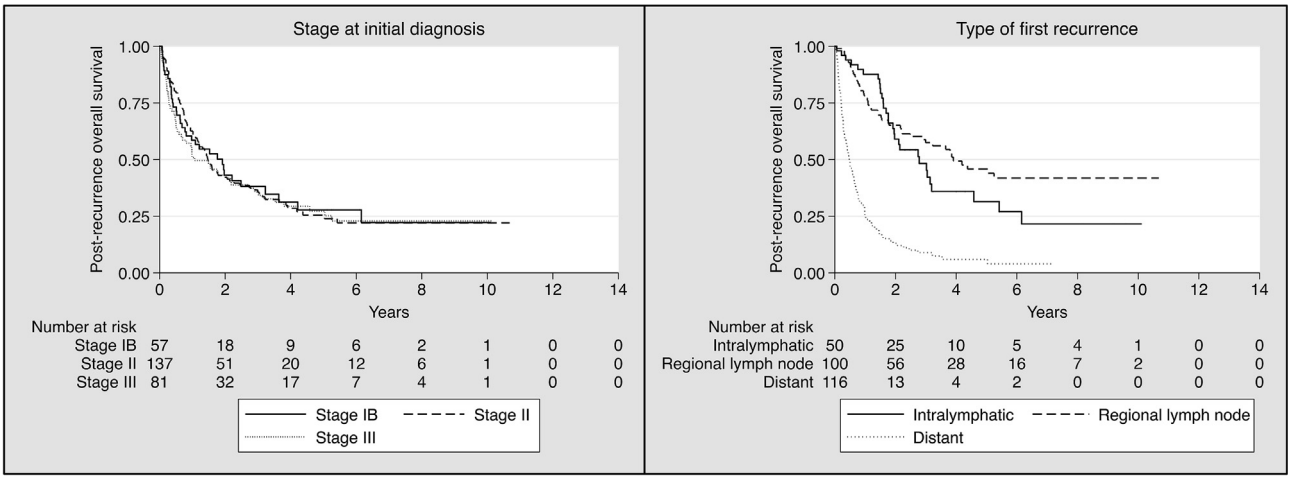

Fig. 4. Kaplan-Meier curves for post-recurrence overall survival.

recurrence; patients with distant metastases had a shorter post-recurrence OS (median: 0.5 years) than patients with intralymphatic (2.8 years) and regional lymph node metastases (3.9 years).

To our knowledge, the rate of recurrence in patients with stage IB was only reported by one previous study [17]. Their rate was, however, higher than the rate in our study (18% versus 8%). The rate of recurrence in patients with stage II was more comparable to the rates reported by previous studies (33–40%) [5,9,17]. One of these studies also reported comparable results for patients with stage III [5]. In contrast, three other studies reported much higher rates in these patients, ranging from 66% to 82% [9,10,15]. On the one hand, this may be due to differences between the patient populations. In two of the three studies, patients were treated in a melanoma referral center and, therefore, their patients may have been at a higher risk of disease recurrence. For example, compared to our study, the study by Romano et al. [10] had relatively more patients with stage IIIC (26% versus 17%). On the other hand, the difference in the rate of recurrence between the studies may be due to differences in initial staging (e.g., use of sentinel lymph node biopsy) and follow-up guidelines. Unfortunately, only one study, the study by Romano et al. [10], reported the follow-up schedule. Their patients had three monthly visits during the first two years and half-yearly thereafter. In contrast, our patients had three monthly visits during the first year, half-yearly visits during the second year, and yearly visits up until the fifth year. Although all follow-up guidelines aim to identify disease recurrence at its earliest stage, there is still considerable variation in follow-up schedules and a lack of data to support them [18,19].

The type of first recurrence is an important prognostic factor for post-recurrence survival. Previous studies showed that patients with local recurrences or intralymphatic metastases had a longer post-recurrence survival than patients with regional lymph node or distant metastases [5,8,10,13]. In accordance to these studies, the patients with distant metastases in our study had the shortest post-recurrence survival. In contrast, however, the observed post-recurrence survival was longer for patients with regional lymph node metastases than for patients with intralymphatic metastases. This may be due to the age of the patients at the moment of diagnosis of the first recurrence. The median age for patients with intralymphatic metastases was 71 years compared to 58 years for patients with regional lymph node metastases. It is most likely not related to the number of patients who developed distant metastases after first developing intralymphatic or regional lymph node metastases, because this was comparable between both patient groups (40% and 45% for patients with intralymphatic and regional lymph node metastases, respectively). Post-recurrence survival appeared to be independent from the stage at initial diagnosis. Although the median post-recurrence OS was somewhat longer for patients initially diagnosed with stage IB (1.9 years) than for patients initially diagnosed with stage II (1.5 years) and III (1.1 years), the Kaplan-Meier curves largely overlapped.

Our study has some limitations. First, the population in the six study hospitals covered only 11% of the total Dutch melanoma population. The population in the study hospitals was, however, considered to be a good representation of the Dutch melanoma population because the baseline (patient and tumor) characteristics and survival of both populations were comparable (Supplemental Table and Supplemental Figure). Second, to ensure the feasibility of the study, we did not collect data on disease recurrence for patients with stage IA. Although Francken et al. [17] reported that 5% of these patients would have developed disease recurrence, we assumed that disease recurrence in patients with stage IA would not be related to survival. According to the NCR, the ten-year melanoma-specific survival rate of these patients is 100% [2].

Our study also has important strengths. First, in contrast to other studies [8,9], we evaluated the risk of disease recurrence while taking into account the risk of dying without disease recurrence. This resulted in a five-year cumulative incidence of disease recurrence of 7% for patients with stage IB, 30% for patients with stage II, and 47% for patients with stage III. In the presence of competing risks (e.g., dying without disease recurrence), the risk of an event of interest (e.g., disease recurrence) may be overestimated if the competing risk is not taken into account [20]. Therefore, our results provide a more precise estimate of the risk of disease recurrence at the moment of diagnosis compared to what is currently available in the literature. Second, we evaluated survival from diagnosis as well as post-recurrence survival, which provided insight into the impact of disease recurrence on survival. Our results showed that, depending on the type of first recurrence, survival decreases after developing disease recurrence.

In conclusion, a substantial number of patients with localized and regionally advanced melanoma developed disease recurrence. Of these patients, a considerably high proportion developed distant metastases which had a great impact on survival. Identifying disease recurrence at its earliest stage is crucial because metastatic

melanoma remains incurable for most patients. Further research on the most optimal follow-up schedule for melanoma patients is, therefore, of utmost importance.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.01.225.

Conflict of interest and source of funding

There are no conflicts of interest for the conduct of this manuscript. The study was funded by GlaxoSmithKline.

References

[1] International Agency for Research on Cancer. Globocan 2012. Cancer today IARC. May 2018, http://gco.iarc.fr/today/explore; 2016.
[2] Netherlands Comprehensive Cancer Organisation. Dutch cancer Registry. May 2018, https://www.cijfersoverkanker.nl/selecties/dataset_1/img5b279c46b8f97; 2017.
[3] Cancer Research UK. Skin cancer incidence statistics. 2016. May 2018, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer.
[4] Svedman FC, Pillas D, Taylor A, Kaur M, Linder R, Hansson J. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe - a systematic review of the literature. Clin Epidemiol 2016;8:109–22.
[5] Hohnheiser AM, Gefeller O, Göhl J, Schuler G, Hohenberger W, Merkel S. Malignant melanoma of the skin: long-term follow-up and time to first recurrence. World J Surg 2011;35:580–9.
[6] Lyth J, Falk M, Maroti M, Eriksson H, Ingvar C. Prognostic risk factors of first recurrence in patients with primary stage I-II cutaneous malignant melanoma-from the population-based Swedish melanoma register. J Eur Acad Dermatol Venereol 2017;31:1468–74.
[7] Meier F, Will S, Ellwanger U, Schlagenhauff B, Schittek B, Rassner G, et al. Metastatic pathways and time courses in the orderly progression of cutaneous melanoma. Br J Dermatol 2002;147:62–70.
[8] Mervic L. Time course and pattern of metastasis of cutaneous melanoma differ between men and women. PLoS One 2012;7, e32955.
[9] Rockberg J, Amelio JM, Taylor A, Jörgensen L, Ragnhammar P, Hansson J. Epidemiology of cutaneous melanoma in Sweden—stage-specific survival and rate of recurrence. Int J Cancer 2016;139:2722–9.
[10] Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol 2010;28:3042–7.
[11] Salama AK, de Rosa N, Scheri RP, Pruitt SK, Herndon II JE, Marcello J, et al. Hazard-rate analysis and patterns of recurrence in early stage melanoma: moving towards a rationally designed surveillance strategy. PLoS One 2013;8, e57665.
[12] Soong S, Harrison RA, McCarthy WH, Urist MM, Balch CM. Factors affecting survival following local, regional, or distant recurrence from localized melanoma. J Surg Oncol 1998;67:228–33.
[13] Tas F, Erturk K. Recurrence behavior in early-stage cutaneous melanoma: pattern, timing, survival, and influencing factors. Melanoma Res 2017;27:134–9.
[14] Tejera-Vaquerizo A, Barrera-Vigo M, Fernandez-Canedo I, Blazquez-Sanchez N, Mendiola-Fernandez M, Fernández-Orland A, et al. Longitudinal study of different metastatic patterns in the progression of cutaneous melanoma. Actas Dermo-Sifiliográficas (English Edition) 2007;98:531–8.
[15] White RR, Stanley WE, Johnson JL, Tyler DS, Seigler HF. Long-term survival in 2,505 patients with melanoma with regional lymph node metastasis. Ann Surg 2002;235:879–87.
[16] Michielin O, Hoeller C. Gaining momentum: new options and opportunities for the treatment of advanced melanoma. Cancer Treat Rev 2015;41:660–70.
[17] Francken A, Accortt N, Shaw H, Colman M, Wiener M, Soong S, et al. Follow-up schedules after treatment for malignant melanoma. Br J Surg 2008;95:1401–7.
[18] Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Bastholt L, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline—Update 2016. Eur J Cancer 2016;63:201–17.
[19] Trotter SC, Sroa N, Winkelmann RR, Olencki T, Bechtel M. A global review of melanoma follow-up guidelines. J Clin Aesthet Dermatol 2013;6:18–26.
[20] Putter H, Fiocco M, Geskus R. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389–430.