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Patterns of Recurrence of Cutaneous Melanoma: A Literature Review

Dominga Peirano[1], Francisca Donoso[1], Sebastián Vargas[1], Leonel Hidalgo[1], Rosario Agüero[1], Pablo Uribe[1,2], Sebastían Mondaca[2,3], Cristian Navarrete-Dechent[1,2]

1 Department of Dermatology, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
2 Melanoma and Skin Cancer Unit, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
3 Department of Medical Oncology, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

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Corresponding Author: Cristian Navarrete-Dechent, MD, Department of Dermatology, Escuela de Medicina, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, 6th floor, Santiago, Chile 8330077. Phone: +56-2-2435 3574 E-mail: ctnavarr@gmail.com

ABSTRACT The incidence of melanoma has been dramatically increasing over the last decades. Melanoma is considered to have a high metastatic potential and it can progress via lymphatic vessels or through hematogenous metastasis. Different patterns of recurrence have been described, namely, local, satellite, and in transit metastasis (LCIT), lymphatic metastasis, and systemic metastasis. With a more advanced melanoma stage at diagnosis, there is a higher risk for systemic metastasis in comparison to LCIT; in contrast, early-stage melanoma tends to recur more frequently as LCIT and less commonly as systematic metastasis. The aim of this review was to summarize the patterns of recurrence of cutaneous melanoma, giving the clinician a practical summary for diagnosis, prognosis, and surveillance. There is a knowledge gap of the common patterns of recurrence that needs to be addressed to better identify patients at high risk of disease recurrence and personalize surveillance strategies as well as patient counseling.

Introduction

The incidence of melanoma has been dramatically increasing worldwide over the last two decades [1,2]. It is the fifth most common cancer in the U.S. and the ninth in Europe[3]. In 2023, it was estimated that there would be 89,070 new melanoma cases in the United States (US) with 7,990 patients dying of the disease [2]. Patients with early-stage cutaneous melanoma (i.e. stages I and II) are generally considered to have an excellent prognosis. Data from the Surveillance, Epidemiology, and End Results (SEER) Program suggests that 99.5% of patients with localized melanoma, 70.6% regional melanoma, and 31.9% of those with distant metastases, will be alive at 5 years [4]. Cutaneous melanoma is considered to have a high metastatic potential and it can have lymphatic metastasis or hematogenous metastasis [5]. Specifically, it can metastasize as local, satellite, and in transit metastasis (LCIT), on lymph nodes, or as distant metastasis [5–8]. The presence of regional lymph node metastatic disease is a significant predictor of outcome in melanomas as it is associated with a 50% reduction in survival compared to patients without nodal involvement [3,9].

There is limited research analyzing the patterns of recurrence in patients with primary localized cutaneous melanoma. Meier et al study in 2002 traced the metastatic pathways of 3,001 patients with primary cutaneous melanoma from 1976-1996. Of the patients who had disease confined to the primary tumor at diagnosis (i.e. stages I and II), 15.5% developed metastasis during the study period [6]. Another study conducted in 1999 by Cohn et al. identified 569 of 2493 patients with recurrent melanoma and demonstrated a 5-year survival rate of 82% and 30% among those with a primary local versus regional recurrence, respectively [10]. Furthermore, current guidelines are fairly vague as to how aggressively we should follow up patients with localized disease (i.e. stage I and II), with most advocating only routine skin examinations at various intervals for the first 5 years. Surveillance guidelines, in general, and melanoma patients specifically, are often follow-up based on low-level evidence. Additionally, despite clinical guidelines, practice patterns tend to vary across different institutions and countries [11–14].

Given the increasing incidence of cutaneous malignant melanoma and the recent changes in the treatment landscape, it is important to understand stage-specific recurrence patterns [15]. In the current era of immune checkpoint inhibitors and targeted therapies, early detection of melanoma recurrences is important, as it can lead to more effective and manageable treatment options.

Objective

The aim of this review was to evaluate the recurrence patterns of cutaneous melanoma, regarding the time of follow-up, time of detection of the recurrence, and the most frequent site of recurrence, giving the clinician a practical summary for diagnosis, prognosis, and surveillance.

Methods

A literature narrative review of articles published in PubMed between the years 2000 to 2022 was conducted. The keywords were “Melanoma” OR “Cutaneous melanoma” AND “Recurrence” OR “Relapse” AND/OR “Patterns”. We included all studies in English and/or Spanish. Exclusion criteria were non-skin melanomas, stage IV melanoma only, studies published before the year 2000, studies reporting the local and regional recurrence together as one group, and case reports and case series with less than 10 patients. From the remaining results, study type, number of patients, stage of melanoma at diagnosis and substage if they reported (e.g IA, IIB, IIC), median follow-up, mean recurrence time (in months), recurrence site, recurrence predictors, and survival rate were recorded. For the study purposes, ‘recurrence’ was defined as the return of the melanoma after initial treatment and after a period of time during which the cancer was not detected. ‘Progression’ was defined as melanoma growing or spreading without ever having gone away completely. The recurrence sites were divided into local, satellite, and in transit metastasis (LCIT), lymph nodes/nodal, and systemic metastasis. We also described the sites of systemic metastasis, if reported. The recurrence detection method was classified into patient symptoms (i.e. detected by the patient), physical examination (e.g. palpation, visual examination), and images (e.g. PET-CT). Overall survival (OS) was presented as a percentage rate at 3 or 5 years.

Results

The overall information is summarized in Tables 1-4.

Follow-up and Recurrence Type

The rate of melanoma recurrence was determined by the median follow-up time reported in different studies. Most studies have shown similar recurrence timing patterns. Across all stages, Meyers et al reported a recurrence rate of 36%, with a median time of recurrence of 14 months [16]. O ‘Connell et al and Berger et al reported lower recurrence rates of 24% and 29.5%, respectively [1,3]. Barbour et al reported the highest rate of recurrence of 45% in their series [17].

Table 1. Patients' demographics and melanoma diagnosis details.

Study	Year of publication	Summary of the study	Country	Number of patients of the study (n)	Mean Age (y, range or SD)	Gender (Male/ Female)	Stage	Mean follow up (months)
Meier F, et al.	2002	Retrospective	Germany	3001	-	-	I-II	120
Meyers O, et al.	2008	Retrospective	USA	118	63,5	41 (35%) Female 77 (65%) Male	II-III	44
Barbour S, et al.	2015	Prospective	Australia	173	Group 1: 61 (15–92) Group 2: 61 (20–88)	19 (18%) Female 88 (82%) Male	IIIB-IIIC	32
O Connell E, et al.	2015	Retrospective	Ireland	164	51.2 (±14.1)	88 (53.7%) Female 76 (46.3%) Male	I-II	75
Svedman F , et al.	2016	Systematic Review .	Multicenter	152.422	-	-	I-III	-
Sparks DS, et al.	2016	Retrospective	Australia	107	72.1 (58–80)	25 (23.4%) Female 82 (76.6%) Male	I-III	30,5
Berger AC, et al.	2017	Retrospective	USA	581	63.5 (11–91)	221 (38%) Female 360 (62%) Male	II	-
Lee AY, et al.	2017	Retrospective	USA	738	62 (17–91)	284 (38.5%) Female 454 (61.5%) Male	II	52
Namin AW, et al.	2018	Retrospective	USA	168	62	42 (25%) Female 126 (75%) Male	I-II	-
Leeneman B, et al.	2019	Retrospective	Netherlands	1397	Stage I 54 (43–64) Stage II 63 (50–74) Stage III 58 (45–69)	1754 (56.7%) Female 1339 (43.2%) Male	I-III	65
Thomas DC, et al.	2019	Retrospective	Multicenter	6305 (5351 SLN negative)	-	2310 (43%) Female. 3041 (57%) Male	I-II	32,1
Bartlett EK, et al.	2020	Prospective	USA	370	61 (5–95)	145 (39%) Female 225 (61%) Male	III	33
Bleicher J, et al.	2020	Retrospective	USA	580	62 (48–74)	228 (39.3%) Female 352 (60.7%) Male	II	59
Oh Y, et al.	2020	Retrospective	Corea	340	57,94	195 (57.4%) Female 142 (42.6%) Male	I-II	46,2
Eggermont M, et al.	2021	Clinical Trial	Multicenter	1019 (514 pembrolizumab, 505 placebo)	251 (25%) > 65 years	Female 391 (38%) Male 628 (62%)	III	42,3
Ertekin S, et al.	2021	Retrospective	Spain	3786	58.27 (± 16.75)	330 (42.1%) Female 454 (57.9%) Male	I-III	-
Luke J, et al.	2022	Clinical Trial	Multicenter	976 (487 group 1, 489 group 2)	61	Female 387 (40%) Male 589 (60%)	IIB-IIC	20,9

Table 2. Melanoma recurrence details and method of detection.

Study	Recurrence of melanoma n(%)	Mean time of recurrence (months)	Mean time of LCIT recurrence (months)	Mean time of LN recurrence (months)	Mean time of systemic recurrence (months)	Detection of recurrence
Meier F, et al.	466/3001 (15%)	-	17	16	25	-
Meyers O, et al.	43/118 (36%)	14	-	-	-	Patient self-report (67%) Physical examination (26%) Images (7%)
Barbour S, et al.	78/173 (45%)	-	-	-	-	-
O Connell E, et al.	40/164 (24%)	39,5	-	-	-	-
Svedman F , et al.	-	-	-	-	-	-
Sparks DS, et al.	38/107 (35.5%)	11,8	-	-	-	-
Berger AC, et al.	171/581 (29.4%)	-	-	-	-	Patient self-report (39%) Physical examination (32%) Images (21%)
Lee AY, et al.	219/738 (29.6%)	IIA (195.1) IIB (unknown) IIC (85.9)	-	-	-	Patient self-report (59%)
Namin AW, et al.	33/168 (20%)	17	8	13,5	18,3	-
Leeneman B, et al.	275/1397 (20%)	IB (34) II (18) III (12)	-	IB 36) II (9.6) III (6)	IB (37) II (26) III (13)	-
Thomas DC, et al.	558/5351 (10.4%)	-	16,7	18,6	31,2	-
Bartlett EK, et al.	158/370 (42.7%)	12	-	-	-	Patient self-report (29%), Physical examination (20.3%), Images (39.9%).
Bleicher J, et al.	158/580 (27.2%)	-	-	-	-	Patient self-report (60.1%) Physical examination (12.0%) Images (27.3%)
Oh Y, et al.	92/340 (27.1%)	16,3	-	-	-	-
Eggermont M, et al.	199/514 (39%) Group 1 287/505 (53%) Group 2. Total 47.6%	-	-	-	-	-
Ertekin S, et al.	Total: 784/3786 (20.7%) Stage I (21%) Stage II (33%) Stage III (45%)	Total: 21 Stage I (40) Stage II (22) Stage III (14)	17,5	25,5	25	-
Luke J, et al.	187/976 (19%)	-	-	-	-	-

Table 3. Melanoma recurrence location details and predictors of recurrence.

Study	Location of recurrence	Recurrence LCIT (n)	Recurrence LN (n)	Recurrence Systemic (n)	Predictors of recurrence
Meier F, et al.	LCIT (21.7%) LN (50.2%) Systemic (28.1%)	101	234	131	Location of initial tumor (p<0.001) Tumor thickness (p=0.028)
Meyers O, et al.	LCIT (49%) LN (16%) Systemic: (35%)	21	7	15	-
Barbour S, et al.	LCIT (14%) LN (8%) Systemic (78%)	Group 1: 5 Group 2: 6	Group 1: 5 Group 2: 1	Group 1: 33 Group 2: 28	-
O Connell E, et al.	LCIT (30%) LN (30%) Systemic: (40%)	12	12	16	Nodular Subtype (p<0.05) Tumor thickness (p<0.001)
Svedman F, et al.	-	-	-	-	-
Sparks DS, et al.	LCIT (16%) LN (12%) Systemic (15%)	17	13	16	-
Berger AC, et al.	-	56	52	63	Male sex (p=0.0018) T classification (p=0.0049) Ulceration (p=0.0016)
Lee AY, et al.	-	80	50	81	-
Namin AW, et al.	LCIT (18%) LN (18%) Systemic (49%)	6	6	21	-
Leeneman B, et al.	-	59	100	116	-
Thomas DC, et al.	-	221	109	220	**For LCIT recurrence:** age, anatomic location, thickness (all p<0.05) **For LN recurrence:** age and thickness (all p<0.05) **For systemic recurrence:** anatomic locations, thickness, ulceration, and lymphovascular invasion (all p<0.05)
Bartlett EK, et al.	-	45	62	51	-
Bleicher J, et al.	LCIT (19.6%) LN (29.8%) Systemic (50.6%)	31	47	80	Age (p< 0.05) Stage (p<0.05) Breslow (p< 0.01)
Oh Y, et al.	-	29	49	28	Male sex (p=0.030) Breslow >1 mm (p=0.008)
Eggermont M, et al.	-	-	-	Group 1 126 (25%) Group 2 194 (38%)	-
Ertekin S, et al.	LCIT. (50.1%) LN - Systemic (49.9%)	393	98	293	-
Luke J, et al.	-	-	-	Group 1:31 Group 2 : 60	-

Table 4. Melanoma survival and additional details.

Study	Survival	Overall Survival (months at 5 years)	Overall survival % at 5 years	Disease free survival (n) at 5 years	Disease free survival (%) at 5 years	Additional details
Meier F, et al.	-	-	-	-	-	
Meyers O, et al.	-	22 (LN and LCIT) 7 (Systemic)	-	-	-	
Barbour S, et al.	-	-	53	80	46%	-
O Connell E, et al.	23.5% from the diagnosis	6	-	-	-	-
Svedman F , et al.	-	-	Stage I (95%–100%) Stage II (65%–92.8%) Stage III (41%–71%) Stage IV (9%–28%)	-	-	-
Sparks DS, et al.	-	-	47	-	47	First site being lungs (4), brain (3), liver (2), subcutaneous (1), bone (1), and synchronous metastases to multiple sites (6)
Berger AC, et al.	IIA (57%) IIB (57%) IIC (40%) at 5 years	-	-	-	-	-
Lee AY, et al.	-	Stage IIA (87%) Stage IIB (78%) Stage IIC (69%)	-	-	-	Lung was the most frequent site of systemic relapse in all substages (n = 11, 11, and 13 for stage IIA, IIB, and IIC, respectively). The second most frequent site was brain for IIA (n = 9) and IIC (n = 5), and liver for IIB (n = 4). Three IIA patients had a rare site of distant metastasis— two to the larynx, and one to the heart.
Namin AW, et al.	92%	-	.	135	85	-
Leeneman B, et al.	-	Stage IB 1.9 years (95% CI: 0.8-3.2) Stage II 1.5 years (95% CI: 1.1-2.1) Stage III 1.1 years (95% CI: 0.6-2.2).	Stage IB (41%) Stage II (42%) Stage III (43%) at 2 years	-	-	-

Thomas DC, et al.	-	-	86.9%	.	-	-
Bartlett EK, et al.	-	-	-	-	-	-
Bleicher J, et al.	-	-	Stage IIA (82.6%) Stage IIB (71.5) Stage IIC (60.3%)	-	-	Distant recurrence, 29 (36.3%) patients had pulmonary metastases, 17 (21.3%) had brain metastases, 9 (11.3%) had intraabdominal metastases, 6 (7.5%) had bone metastases, 7 (8.8%) had multiple sites of primary recurrence, and 12 (15.0%) had distant metastasis at another location.
Oh Y, et al.	-	-	-	-	-	The most common site of distant metastasis was the lung, and the median latency of lung metastasis was 19.7 months.
Eggermont M, et al.	-	-	-	Stage III A 62 (group 1) 54 (group 2). Stage III B 164 (group 1) 123 (group 2) Stage III C 115 (group 1) 83 (group 2)	Stage IIIA: 80.8% (95% CI 69.7–88.2) in group 1 and 70.8% (58.7–79.9) in group 2 Stage IIIB disease, 68.1% (61.6–73.8) in group 1 and 51.0% (44·2–57·4) in group 2. Stage IIIC disease 55,8% (48.1–62.8) in group 1 and 39.2% (32.2–46.1) in the group 2.	-
Ertekin S, et al.	-	-	-	-	-	-
Luke J, et al.	-	-	-	-	-	-

Frequency and patterns of melanoma recurrence were highly stage dependent. Studies grouping stage I and II melanoma patients have estimated 1 and 10-year recurrence rates at approximately 9% and 23% respectively, with increasing risk dependent on stage [8,18,19]. When stratified by AJCC 7th substage, a large retrospective study conducted at Memorial Sloan Kettering Cancer Center found the 5-year risk of recurrence for stage IIA, IIB, and IIC to be 21.6%, 35.1%, and 45.3%, respectively. Substratification of stage III patients in a large retrospective analysis reported an overall 5-year risk of recurrence for stages IIIA, IIIB, and IIIC to be approximately 48%, 71%, and 85%, respectively [8,20]. A recent study from Finland examined the PET/CT follow-up utility, the recurrence rate was 49% in stage IIB and IIC patients. A total of 38% of the melanoma recurrences were loco-regional recurrences (9% LCIT and 29% in lymph nodes) and 61% were systemic recurrences [1,21]. Stage IIC disease behaved similarly to Stage IIIB and IIIC melanoma with the highest risk of recurrence in the first 2–3 years following diagnosis [8,22,23].

Time for Recurrence

The timing for metastasis development in patients with primary cutaneous melanoma must be considered within the context of the above-mentioned melanoma TNM stages. Most of the studies did not report the onset or timing of the recurrence from diagnosis. For those studies that mention it, the majority of metastasis occurs within 3 years of diagnosis [8,20,22,24-26] and recurrence rates were earlier with more advanced stages [3,6,16,21,28-32]. Fusi et al in their study of 250 patients with stage I-II melanoma, reported that 67% of recurrences arose within 2 years and 81% within 3 years of disease [33]. Dicker et al in their study of 1,568 patients with stage I melanoma reported that 80% of recurrences occurred in the first 3 years [26]. Behave et al in their study reported that time to first recurrence occurred at a median time of 17.7 months (range 1.7–53.6) [34]. However, a recent study with long-term follow-up showed that only 82% of recurrences occurred in the first 5 years, 91% in the first 7 years, and some occurring even after 10 years from melanoma diagnosis [35]. Similarly, the mean time for recurrence in Lee et al series was shorter in later stages when compared to early stages (34 months in stage IB vs. 12 months in stage III) [24]. Ertekin et al reported a mean time of recurrence of 40 months in stage I melanoma, 22 months in stage II melanoma, and 14 months in stage III melanoma [32]. Even more, some studies reported the time to recurrence according to the initial type of recurrence (e.g. LCIT vs. lymph nodes vs. systemic). Systemic recurrences tend to appear later when compared to local recurrences. The mean time to recurrence in Meier et al study was 17 months for the LCIT group, 16 months for the lymph node group, and 25 months for the systemic recurrence group [6]. Also, Namin et al study showed a mean time to recurrence of 8 months in the LCIT group, 13.5 months in the LN group, and 18.3 in the systemic recurrence group [31].

Type and Site of Recurrence

In all (without accounting for melanoma stage at diagnosis), the most common melanoma recurrence type was systemic recurrence in all studies [1,3,17,22,24,29–31]. O'Connell et al reported that 40% of melanoma recurrences were systemic [3]; for Namin et al and Bleicher et al, recurrences were systemic in 49% and 50.6%, respectively. In prospective randomized studies evaluating melanoma surgical margins, LCIT recurrence rates (or surgical site recurrence) were as low as 2-5%, despite wide or narrow surgical margins used [36]. Overall, LCIT recurrences are low compared to systemic or nodal recurrences.

When systemic recurrence occurs, the most common site of distant metastasis was the lung followed by the brain, liver, and bone [22,24,27,28,31]. The second most frequent recurrence site was LCIT [6,32]. This is also in line with studies evaluating systemic therapies where systemic recurrences were the most frequent [37]. In 2020, the Checkmate 238 trial concluded that the lung, liver, and brain were the most common sites of first distant metastasis (seen in 24%, 13%, and 10% of patients, respectively) for patients with resected stage IIIB-C disease [38].

When evaluating recurrence based on melanoma stage, recurrences were more likely to be systemic and less likely to be nodal or LCIT, as the AJCC stage increases [39]. A retrospective study of 466 patients, detected the proportion of recurrences to be systemic in 48% of stage II, 68% of stage III, and 77% of resected stage IV patients [40]. This trend was also related to substage as patients with stage IIA and IIC had a systemic recurrence rate of 34% and 52%, respectively [40,41]. A study by Romano et al concluded that as substages increased from IIIA to IIIB to IIIC, the proportion of LCIT recurrence as the site of first relapse progressively decreased from 32%, 30%, and 22%, respectively [20]. Similarly, the proportion of initial relapse in lymph nodes decreased (28%, 19%, and 17%) and the proportion of initial relapse as a systemic recurrence increased as substage progressed (40%, 51%, and 61%) [20]. Leeneman et al, however, showed that lymph nodes were the most frequent site of recurrence [29] and in Lee et al study, LCIT was the most common recurrence site (12%) [24]. These differences might be explained by different inclusion criteria and different representation of melanoma stages as well as specific clinical and histopathological details.

Recurrence Detection Method

There is relevance to the modalities for melanoma recurrence detection (i.e. clinical examination vs imaging). Some

studies have reported the melanoma recurrence detection modality: a) symptoms/self-reported by the patient, b) by physician examination (i.e. physical examination), or c) by imaging (e.g. ultrasound, PET-CT, among others). The most frequent modality for detection of recurrence was patient self-report across most studies (mainly by symptoms) [1,16,22,24]. Meyers et al study reported that melanoma recurrence detection was by patient self-reports in 67%, by clinical examination in 26%, and by imaging in only 7% of cases [16]. In Lee et al series, 59% of recurrences were detected by patient self-report (symptoms) and similarly, in Bleicher et al series, 60% of recurrences were detected by patient self-report [22,24]. Based on this data, it appears to be mandatory to directly question patients for specific symptoms (e.g. headache, dyspnea, pain, bumps, or asthenia) during follow-up after melanoma treatment. This should be in addition to melanoma guidelines-directed imaging and other complementary testing and should not be overlooked or underestimated.

Recurrence Predictors

Several risk factors are associated with or predict the risk of melanoma recurrence. The most frequent predictors of recurrence were Breslow thickness and male sex [1,3,6,22,42]. Meier et al showed that the location of the initial tumor (trunk in men and lower extremities in women) and Breslow thickness were the main predictors of recurrence [6]. O'Connell et al reported that recurrence predictors were nodular histologic subtype and Breslow thickness [3]. Similarly, Bleicher et al showed that age, male sex, stage, and Breslow thickness as important recurrence factors [22]. Berger et al series included recurrent factors: Male sex, T- classification, and ulceration as predictors [1]. Thomas et al series evaluated risk factors for specific recurrence patterns. For LCIT recurrence: age, anatomic location, Breslow thickness; for lymph node recurrence: age and Breslow thickness; and for systemic recurrence: anatomic location (head and neck or trunk), Breslow thickness, ulceration, and lymphovascular invasion [42].

Overall Survival: Role of Recurrent Disease

The patterns of recurrence tend to impact melanoma overall survival (OS); therefore, careful understanding of recurrence type can help with patient management and counseling: The sole occurrence of recurrent disease (irrespective of type) is associated with a worse prognosis. Meyers et al study showed that the median survival was 22 months for melanoma recurrences in the LCIT-lymph node group and 7 months for the systemic recurrence group [16]. Leeneman et al showed a mean OS of 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 that recurred [29].

Sparks et al reported an OS of 47% at 5 years and Thomas et al an OS of 86.9% at 5 years after recurrence [27,42]. O'Connell et al reported an OS of 6 months (range of 1-126 months) at 5 years in the recurrent melanoma group when compared to the non-recurrent group [3]. Leeneman et al also found a two-year post-recurrence survival rate of 41%, 42%, and 43% for patients initially diagnosed with stages IB, II, and III, respectively. By the type of first recurrence, median post-recurrence OS was longer for patients with lymph node metastasis (3.9 years; 95% CI: 2.5-Not Reached) than for patients with LCIT (2.8 years; 95% CI: 1.9-4.6) and distant metastasis (0.5 years; 95% CI: 0.3-0.6)[29].

Conclusions

In this review, we have summarized the patterns of recurrence of primary cutaneous melanoma in various studies and populations. The overall recurrence rate ranged from approximately 20% to 40%, with systemic recurrence, particularly to the lungs, being the most frequent pattern. The primary predictors of recurrence were Breslow thickness and male sex. Notably, patient self-report, primarily based on symptoms, was the most frequent method of recurrence detection. This particular finding underscores the importance of patient education regarding signs and symptoms for the early detection of melanoma recurrence or progression. Directly questioning about specific signs and symptoms during each visit is highly relevant. This simple strategy should not be underestimated.

Current Melanoma guidelines lack precision regarding optimal follow-up modalities and when to order specific cross-sectional imaging studies (e.g. computed tomography, PET-CT). Moreover, there is also a wide variation in recommendations among different melanoma guidelines [12,13,43,44]. For example, the National Comprehensive Cancer Network (NCCN) does not recommend imaging in stages I and II in the absence of symptoms. For asymptomatic patients with stages IIB and IIC, NCCN guidelines do not strongly recommend cross-sectional imaging. In contrast, European guidelines recommend cross-sectional imaging from stage IIC onwards but recommend nodal ultrasound from stage IB and above [43]. Given these variations in the specific recommendations, a comprehensive understanding of recurrence patterns is paramount when deciding a detailed and individualized follow-up plan for specific patients [1]. Additionally, a detailed understanding of melanoma recurrence patterns might have a role in adjuvant treatment selection. Recently, the approval of adjuvant treatment with immune checkpoint inhibitors and targeted therapies by both the US Food and Drug Administration (FDA) and the European

Medicine Agency (EMA) have significantly changed melanoma management [37]. The projected increase in the use of adjuvant systemic therapy might also lead to changes in melanoma recurrence patterns among treated patients when compared to those described in this study.

Strict follow-up and patient education play a critical role in detecting melanoma recurrences. Due to the higher prevalence of regional lymph node recurrences in early-stage melanoma, ultrasound may prove to be a valuable and cost-effective strategy for recurrence detection in early-stage melanoma [1]. Conversely, for patients with more advanced disease at diagnosis, cross-sectional full-body imaging (e.g. PET-CT) might be of benefit due to the more frequent systemic metastasis. This knowledge gap needs to be addressed in order to better identify patients at high risk of disease recurrence and personalize surveillance strategies [11,24,45]. Recognizing melanoma recurrence patterns can aid in the design of active surveillance strategies that have the potential to modify clinical follow-up plans.

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