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ORIGINAL ARTICLE
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Synchronous Melanoma: Definition, Prognosis, and Implications. A Comprehensive Review of Literature

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Background: Although multiple primary melanomas (MPMs) have been reported in the literature, the subgroup of synchronous melanomas (SMs) remains understudied.
Methods: We conducted a comprehensive systematic review of the English literature from 1972 to 2023 to characterize SM. Our objective was to clarify the definition, determine incidence and prognosis, and present recommendations.
Results: We found 18 case series articles and six case reports that met our criteria. Twelve of eighteen studies defined SM as a second primary melanoma identified within 1 month. The total number of SM patients reported was 1083. The cumulative percentage of MPM in total melanoma patients was 2.9 %, and the cumulative percentage of SM patients in MPM patients was 31.3%. SM patients trended toward higher body anatomical concordance, older age, and male sex. Despite limited data, SMs do not show a worse prognosis for patients compared with single melanomas.
Conclusions: Despite a lack of consensus in the past, we recommend that SM be defined as a second primary melanoma detected within 1 month of the initial diagnosis. SMs comprise almost one-third of MPM cases and do not seem to carry any worse prognosis than the patients presenting with single melanoma. We believe older age and male sex may be more prone to SM. We recommend patient education, self-skin evaluations and TSE at initial and follow-up visits. Neither randomized controlled trials nor meta-analyses on SM exist. Ideally, further studies with a large cohort of patients are needed to accurately define SM. *(Plast Reconstr Surg Glob Open 2023; 11:e5272; doi: 10.1097/GOX.0000000000005272; Published online 13 September 2023.)*

INTRODUCTION

Cutaneous melanoma (CM) is a major global health issue.[1] Even though it compromises just 10% of the total cutaneous malignant lesions, it is responsible for more than 90% of deaths.[2] In 1952, Pack was the first to describe the development of more than one primary melanoma in a single patient, now referred to as multiple primary melanoma (MPM).[3] MPM may be classified as synchronous and metachronous.[4] The correlation between the presence of MPM and prognosis has been debated. Studies show that the percentage of patients who develop MPM ranges from 0.2% to 8.6%, out of which 26%–40% develop as synchronous lesions, though the definition of synchronous seems inconsistent.[5–7] About 0.5% of CM patients will present with SM when first seen.[7,8]

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Received for publication May 29, 2023; accepted July 27, 2023.

DOI: 10.1097/GOX.0000000000005272

The bulk of the current literature focuses on MPM, with little attention paid to synchronous melanoma (SM). The aim of this article is to characterize SM and address the controversy in its definition. To this end, we conducted a systematic review of the English literature to answer these questions Here, we report the incidence of SM among MPM patients and identify risk factors, body concordance for the second primary melanoma, dermoscopic features, surveillance recommendations, and SM patient prognosis.

MATERIALS AND METHODS

A systematic literature search was conducted with PubMed, Google Scholar, Medline Ultimate, and Cumulative Index to Nursing and Allied Health Literature databases on February 26, 2023, using the search terms, "melanoma," "synchronous melanoma" "concurrent melanoma," and "synchronous melanoma management" by three reviewers independently. We also used the "related articles" search function to review more articles. All abstracts, studies, and citations were reviewed. We limited the date range of publication from 1972 to 2023. We excluded articles involving noncutaneous melanoma, videos only, and conference abstracts. We also excluded articles in which SM

Disclosure statements are at the end of this article, following the correspondence information.

and treatment were not the focus of the study. If there was disagreement about the suitability of the article, the three reviewers discussed and reached a consensus.

Only relevant peer-reviewed English language articles involving human subjects were included in our final analysis. We evaluated the literature for incidence of MPM and SM, risk factors, dermoscopic features, body concordance, effect on prognosis, and surveillance recommendations. The results were summarized and evaluated to answer our objectives. The data were analyzed in a descriptive manner in accordance with the best practice as described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] We identified 18 case series and six case reports for our analysis (Fig. 1).

Takeaways

Question: Our key question is to characterize synchronous melanomas (SMs).

Findings: A majority of studies defined SM as a second primary melanoma identified within 1 month. In total, 1083 patients have been reported. The total percentage of SM patients in multiple primary melanoma patients was 31.3%. Data do not show a worse prognosis for SM patients compared with single melanomas. Surveillance recommendations include skin self-examination and a total skin examination.

Meaning: Comprehensive skin examination after melanoma diagnosis looks for SM and if present, it is not associated with worse prognosis.

RESULTS

Clarification of Definition

The current definition of SM is arbitrary and inconsistent in the literature. Several studies define SM as a second primary melanoma detected within 1 month of the initial diagnosis of melanoma.[10–21] Other studies define SM as a second primary melanoma detected within 2 months of the initial diagnosis of melanoma.[1,22] Yet others define SM as that occurring within 3 months of the first primary melanoma.[5–7,23]

Dermoscopic Features

Very few studies have compared the dermoscopic features of SM with metachronous melanoma. One case report showed three melanomas from a single patient, with different dermoscopic patterns. Two studies, a case report and a case series, revealed that synchronicity was associated with the occurrence of dermoscopically similar melanomas. This case series of 58 MPM patients showed that most (65%) of the synchronous lesions were similar, compared with 36% of nonsynchronous lesions.[5]

Body Concordance

We wanted to assess the likelihood of a second primary melanoma arising in the same body area as the original lesion. In Slingluff's series, of the 102 MPM patients, only 24 patients reported a second primary melanoma in the same anatomical body part, and 78 on a different body part.[13] Conversely, Manganoni reported development of second primary melanomas in the same anatomic region as the first in 53.2% of the patients.[20]

Sarver et al found that compared with metachronous cohort, the synchronous cohort demonstrated significantly higher concordance between anatomical location for total lesions and lesions of the trunk. Some studies report the highest correlation between locations of the head/neck (80%), the extremities (60%), and the back (47.5%), or no significant correlation at all.[28]

Age and Gender

One study compared invasive melanoma patients diagnosed with one melanoma versus SM. They found that SM patients were diagnosed at an older age than single melanoma patients (Table 1).[8] Sarver et al noted that based on gender, SM had a statistically significantly higher male preponderance compared with solitary melanoma (Table 2).[28]

Incidence

We found 18 case series studies, which included the total number of patients, number of MPM patients, and number of SM patients (Table 3). We used these data to determine the total number of SM cases to date, the cumulative percentage of MPM to total melanoma patients, and the cumulative percentage of SM to MPM patients. The total number of SM patients reported in case series was 1076. The cumulative percentage of MPM in total melanoma patients was 2.9%, and the cumulative percentage of SM to MPM was 31.3% (Table 3).

Nevus spilus (NS) is an uncommon benign skin lesion found in 0.2%–2.3% of the general population. Three of the six SM case reports document SM in the setting of NS (Table 4). The total number of SM patients reported in the literature was 1076 (case series) plus seven (case reports), equaling 1083.

DISCUSSION

Most trained providers, including dermatologists, do not always recognize the early signs of melanoma, judged by the 5% incidence of shave biopsy samples with positive deep margins.[22] Most studies distinguish between primary CM and a cutaneous metastasis by the presence or absence of a junctional component of the lesion.[20]

Definition

Even though there is no consensus regarding the timing of the second primary lesion, 12 of 18 studies define SM as a second primary lesion detected within 1 month of the initial diagnosis of melanoma (Table 5). For uniformity of data, we recommend this timing be considered the standard in the future.

Incidence

Melanoma, like several other cancers of the skin, may be multicentric.[19] Approximately 0.5% of surveillance, epidemiology, and end result CM patients were found to

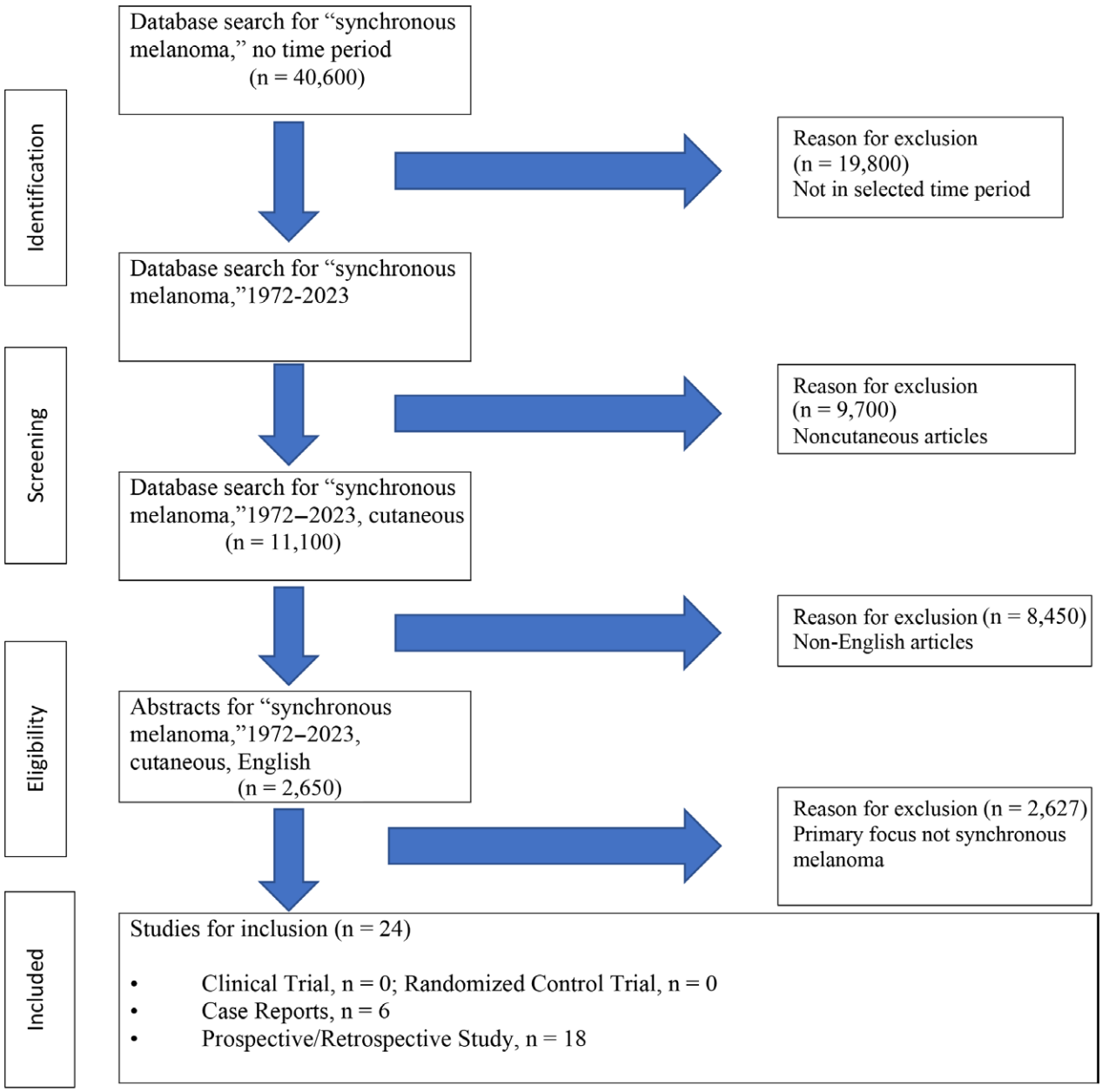

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies.

Table 1. Age in Single and Synchronous Melanoma Patients

	Single Melanoma (N = 5164)	Synchronous (N = 312)	Total (N = 5476)	*P*
Age, median (y)	56.10	64.25	56.32	<0.001

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Table 2. Proportion of Single and SM Based on Gender

Gender	Single (N = 11153)	SM (N = 228)	*P*
Masculine	6033 (54.1%)	149 (65.4%)	0.0002
Feminine	5120 (45.9%)	79 (34.6%)	

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have synchronous second primary melanomas.[16] A total of 2.32% of the surveillance, epidemiology, and end result CM patients eventually developed at least one additional primary CM during their time of follow-up. Approximately 22% of these patients had two synchronous primary CMs.[16] Our cumulative findings were consistent with this data. The cumulative percentage of MPM to total melanoma patients was 2.9%, and the cumulative percentage of SM to MPM patients was 31.3%. To date, 1083 SM patients have been reported in the literature.

Risk Factors

Doubrovsky states that the most important risk factor for a melanoma patient for developing a second primary

Table 3. Synchronous Melanoma Case Series in the Literature

Authors	Year	MPM/Total (%)	Synchronous/ MPM (%)
Cascinelli et al[11]	1975	20/521 (3.8)	8/20 (40.0)
Kang et al[12]	1992	41/2032 (2.0)	16/41 (39.0)
Slingluff et al[13]	1991	283/7145(4.0)	102/283 (36.0)
Ariyan et al[9]	1994	27/423 (6.4)	8/27 (29.6)
Johnson et al[14]	1998	60/1482 (4.0)	18/60 (30.0)
Giles et al[15]	1995	496/14,590 (3.4)	154/496(31.0)
Blackwood et al[16]	2002	441/5540 (8.0)	12/96 (12.5)
Goggins and Tsao[17]	2003	142/61245 (0.2)	31/142 (21.8)
Doubrovsky and Menzies[19]	2003	298/5250 (5.7)	78/298 (26.2)
Ferrone et al[18]	2005	385/4484(8.6)	139/385 (36.1)
Mangononi et al[20]	2007	47/1240 (3.8)	10/47 (21.3)
Savoia et al[4]	2011	277/4297 (6.4)	70/277 (25.3)
Menzies et al[31]	2017	99/2057 (4.8)	13/99 (13.1)
Ungureanu et al[6]	2021	26/699 (3.7)	13/26 (50.0)
Salgüero-Fernández et al[26]	2021	31/1018 (3.0)	12/31 (38.7)
Palacios-Diaz et al[27]	2022	58/646 (9.0)	20/58 (34.5)
Antúnez-Lay et al[8]	2022	533/4703 (11.3)	144/533 (27.0)
Sarver et al[28]	2022	516/11,153 (4.6)	228/516 (44.2)
Cumulative	18 Studies	3780/128,525 (2.9)	1076/3435 (31.3)

Table 4. Synchronous Melanoma Case Reports in the Literature

Author	Year	No. Cases	Age/Gender	No. Lesions
Carli et al[23]	2002	2	62/masculine 64/ masculine	2 2
Piana* et al[29]	2006	1	28/ masculine	3
de Giorgi et al[7]	2007	1	43/feminine	3
Meguerditchian* et al[30]	2009	1	60/masculine	2
Brito* et al[24]	2017	1	83/masculine	4
Nowicka et al[21]	2023	1	77/masculine	3

*NS present.

Table 5. Definition Based on Time of Second Primary Diagnosis after First Diagnosis

SM Definition (Time of Second Primary Diagnosis after First)	No. Studies
Within 1 month	12
Within 2 months	2
Within 3 months	4

melanoma is family history.[19] There are several reports linking NS with SM[24] (Table 3). Furthermore, the risk of a second melanoma increased with older age at diagnosis, a high nevus density, and working outside for more than 10 years.[25] Manganoni et al divided patients into two groups of older and younger than 50 years of age and found that SM appeared more frequently in older patients.[20] Antúnez-Lay et al also found that SM patients were diagnosed at an older age than single melanoma patients.[8] (Table 1). Sarver et al noted that based on gender, SM had a statistically significantly higher male preponderance.[28] (Table 2). We conclude that there is data linking SM with older age, male gender, and NS.

Dermoscopic

Three case studies reported the dermoscopic patterns of multiple SM with different results. In one case, three melanomas from a single patient revealed different dermoscopic patterns, and in the other two, this was associated with the occurrence of dermoscopically similar melanomas. The plausible explanation is that melanomas would result from same causal factor determining the synchronous occurrence of the lesions.[5]

Synchronous versus Metachronous

Slingluff compared synchronous and metachronous lesions for sex, race, family history, primary site of index lesion, other cancer present, primary lesion thickness, histologic findings, Clark level, and ulceration. There was no statistically significant difference in the two groups.[13] The disease-free survival curves for these two groups were indistinguishable.[13] So, at least one study did not find any appreciable difference between SM and metachronous melanoma patients.

Body Concordance

Sarvar et al found that compared with the metachronous cohort, the synchronous cohort demonstrated significantly higher concordance between anatomical location for total lesions and lesions of the trunk.[28] The highest correlation was noted for head/neck (80%) the extremities (60%), and the back (47.5%).[28] The higher-than-expected concordance for SM suggests a "field effect" of susceptibility to malignancy of some anatomic areas.[22] However, some case reports have refuted the concordance issue, with de Giorgi presenting a case where all lesions were in different anatomic areas.[7] Regardless, we believe that this information should guide future surveillance skin examinations to identify new lesions.

Prognosis

In the past, some studies reported poor prognosis of MPM patients,[12,13] but more recently, most authors[10,11,14,25] report an equal or improved prognosis in MPM compared with single melanoma patients.[15,19] The enhanced survival may be explained by the "immunization effect" in animals inoculated with multiple tumors, which slows subsequent tumor progression.[19,28]

However, published research on the prognosis of patients with SM is very limited.[28] Most prognostic studies have excluded these patients because there is some ambiguity surrounding the time to determine synchronicity and, in some cases, exactly which primary melanoma was responsible for the metastatic disease.[8] However, SM patients have been associated with germline *CDKN2A* mutations or MC1R genetic variants but were not associated with worse clinical outcomes.[8] Savoia's experience showed that outcome and survival were not dependent on the number of primary lesions, but according to the American Joint Committee on Cancer Stage.[4]

Surveillance Recommendations

In a case series by Payne, 104 melanomas[30] were discovered on routine total skin examination.[21] In a series by

Aldridge et al, one-third of melanomas detected were not the lesions for which the patients had been referred for the assessment of possible melanomas.[21] A comprehensive skin examination during the initial and subsequent visits is recommended.[14,29] Ungureanu recommends the need for lifetime clinical follow-up and skin self-examination.[6] This may lead to a thinner lesion identified as a second primary melanoma.[30]

Limitations

This study has many limitations. The most obvious is the existence of very sparse data. We had to "tease out" relevant data from existing studies. Another glaring issue is the lack of agreement on the basic definition of SM. Because there is no consensus on the timing to determine synchronicity, it is possible that once the first melanoma is identified, the lack of knowledge of SM may have hampered the continued attentive skin examination.[8,23] Most studies in the United States have relied on the experience of a single institution and may thus suffer from potential selection, referral, or detection biases.[2,4] Finally, there are no large randomized controlled clinical trials or meta-analyses. The lack of specific data points also made any statistical analysis impossible.

CONCLUSIONS

SM remains poorly defined, poorly characterized, and understudied. Despite lack of consensus regarding the definition of SM, we propose that the second primary melanoma be detected within 1 month of the initial diagnosis of melanoma. This is supported by a majority of the studies in the literature. It is imperative that at the time of detection of the CM and at follow-up visits, the whole-body skin should be examined. Patient education and self-skin evaluations should be promoted. A detailed systematic literature review has failed to identify any randomized controlled trials or meta-analyses on this topic. Ideally, further studies with a large cohort of patients are needed to accurately define SM.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

ACKNOWLEDGMENT

The authors thank Lynne M. Bianchi, PhD for assistance in preparation of the article.

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