Imaging Assessment of Interval Metastasis from Melanoma

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Interval metastasis is a particular metastatic category of metastatic localizations in the lymph nodes in patients with melanoma. Interval nodes are generally located at nonregional lymphatic stations placed along the pathway of the spread of melanoma, such as the epitrochlear lymph node station, the popliteal fossa, and the retroareolar station. Imaging techniques for evaluation of patients with interval metastasis from melanoma diseases include ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), lymphoscintigraphy (LS), and positron emission tomography (PET).

1. Introduction

Melanoma accounts for approximately 1% of all skin cancers diagnosed, with a global number of new cases in 2020 of 324,635 and a death toll of 57,043. The highest incidence is in Europe (150,627—46.4%), followed by Northern America (105,172—32.4%) and Asia (23,753—7.3%), with death rates in Europe of 26,360 (46.2%), in Asia of 11,986 (21%) and in Northern America of 8412 (14.7%) [1].

Although melanoma represents only a minority of all skin cancers, this tumor type causes the majority of skin-cancer-related deaths worldwide [1]. In this scenario, an early diagnosis and accurate treatment should improve outcomes and survival [1]. However, today, there are still a significant number of patients who present with or later develop loco-regional or distant recurrence [1]. These patients require ongoing management, and for them, an accurate risk assessment remains an open but critical and key question [1].

Current melanoma treatments include multidisciplinary approaches that involve surgery, chemotherapy, and radiotherapy. Nevertheless, with the exception of those with early-stage disease, patients typically have poor prognoses. Consequently, the need for new treatments has arisen. Immunotherapies and targeted therapies have appeared as promising treatments in trials and in clinical settings [1]. Furthermore, combination therapies are starting to be administered, with favorable outcomes in terms of safety and efficacy [1].

Immunotherapy is based on a complicated process that includes multiple phases, during which there is a stimulation of the immune system. Consequently, a number of immune cells are transferred to the cancer site with the increase in tumor size and/or growth of new lesions [1].

The staging of melanoma is based on clinical and pathological data described by the staging system of the American Joint Committee on Cancer (AJCC) [1][2]. According to this model, routine imaging is not generally recommended in patients with lower risk (stage I and II) when specific signs or symptoms are absent. However, for clinically node-negative patients, an accurate evaluation of regional lymph nodes should be obtained by employing lymphoscintigraphy (LS) and sentinel lymph node biopsy (SLNB), which remain the gold standards of regional lymph node staging [1][2]. With regard to lymph node assessments with ultrasound (US), this tool shows an overall sensitivity of only 24% for the detection of metastases in SLNs mapped on pre-operative LS [3]. This low rate is due to the inability to detect micrometastases. Several studies have shown that the sensitivity improved with increased cross-sectional area (CSA) of lesion deposits, with a significantly better value when the tumor size exceeded 4.5 mm in diameter [3]. So, pre-surgical US cannot replace SN biopsy in the evaluation of regional lymph nodes [3].

A particular category of lymph nodal metastases is interval or intermediate metastasis, which is characterized by the involvement of non-regional lymphatic stations placed along the pathway of the spread of melanoma, such as the epitrochlear lymph node station, the popliteal fossa, and the retroareolar station [4][5][6][7][8]. The incidence of intermediate

metastases in melanoma patients ranges from 3.1% to 7.8%, and, in several patients, these types of lesions could be the only metastatic side [4][7][9][10]. Evidence suggests that the presence of intermediate nodal metastases may represent a negative prognostic feature, since it is associated with an increase in the recurrence and mortality rate [4]. Intermediate metastases should be differentiated from in-transit and satellite metastases, which are both subtypes of superficial metastases. Indeed, metastatic localizations are defined as being "in transit" if they are localized more than 2 cm from the primary melanoma, while they are defined as "satellites" if they are at a distance of less of 2 cm [11].

2. Interval Metastasis from Melanoma

The evaluation of lymph node metastases represents a fundamental point in the staging and follow-up of melanoma. In fact, detection of interval metastases has a crucial role in the management of patients with melanoma, as it has a negative prognostic role associated with an increase in the recurrence and mortality rates [4]. In the case of a negative lymph node biopsy, the patient is staged at level I or II [12]. Instead, a positive lymph node biopsy is indicative of clinical stage III disease and requires baseline imaging to detect the possibility of clinically occult stage IV disease [12].

The usefulness of imaging studies in patients with melanoma generally depends on the stage of the disease. In patients with early-stage disease, surgery is often curative, and, generally, the most commonly used preoperative imaging methods for the evaluation of regional nodal drainage, as well as potential alternative or unpredictable nodal drainage basins, are ultrasound and/or lymphoscintigraphy [12].

In patients with stage III and IV disease, the imaging techniques performed are a contrast-enhanced whole-body CT scan or PET–CT [12]. However, superficial lymph node stations, i.e., the intermediate and in-transit stations, are difficult to detect with CT and MRI, which is mainly due to their small size, while they are more easily detectable in clinical examinations and with US [12].

Therefore, a thorough knowledge of the imaging methods available and the interactions between the clinician and the radiologist are essential for making the correct choices for individual patients, for better management, and to improve treatment and survival [13][14][15][16].

Although US is non-invasive, it involves costs and sophisticated machines. In addition, a high expertise of the physician is mandatory to recognize the normal structures of the lymph nodes draining the lesion. The first sign of metastasis in an SN is habitually identified in the sub-capsular sinus at the point of entry of the afferent lymphatic that drains the primary melanoma. An early metastasis in the sub-capsular sinus is an elongated tumor cell aggregate. Several lesions with a low CSA are not detectable when utilizing the existing technologies. However, in these situations, it is possible to evaluate indirect signs of metastasis, such as an increase in the vascular signal. This feature can be detected by using color Doppler sonography, although other pathological conditions could cause an increase in blood flow in this site. However, US is more sensitive and specific than physical evaluation, and, with respect to other diagnostic tools, such as CT or PET–CT, it is superior for detecting lymph node metastases during surveillance.

Regarding differential diagnoses, many conditions can be associated with the presence of a nodular image within soft tissues, including normal or abnormal vessels, dense scars, and nodal and extra-nodal diseases [17][18][19][20]. Nodal causes include acute lymphadenitis (e.g., cat scratch disease), tubercular lymphadenitis, sarcoidosis-related lymphadenitis, lymphomas, and metastatic lymphadenopathies (especially from melanomas, but also from other cutaneous and non-cutaneous cancers) [17][18][19][21]. Extra-nodal causes include cysts, fluid collections (seromas, hematomas, and lymphoceles), abscesses, tumors (nerve tumors, fibromas, hemangiomas, lipomas, and Merkel cell tumors), cutaneous and subcutaneous hematogenous metastases, and Kimura's disease [17][18][19][21][22][23][24][25][26][27][28][29].

The combination of the patient's history information with features of B-mode and color/power Doppler US usually allows an adequate differential diagnosis [17][22][30].

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