PET / CT in cutaneous melanoma. Staging, treatment control and prognostic factors

Poster No.: C-1316
Congress: ECR 2014
Type: Scientific Exhibit
Authors: J. V. Aguirre¹, G. Schiappacasse², C. Silva²; ¹Santiago/CL, ²Santiago, RM/CL
Keywords: Metastases, Epidemiology, Diagnostic procedure, PET-CT, Soft tissues / Skin, Oncology, Nuclear medicine
DOI: 10.1594/ecr2014/C-1316

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Aims and objectives

Melanoma is a malignant tumor arising from melanocytes which are cells derived from the neural crest, who migrate during embryonic development and are located in the basal layer of the epidermis. They represent 4 % of malignant skin tumors being responsible for 80% of deaths from skin cancer, given its high invasiveness and potential to develop metastases (1-2). Its incidence has been increasing in recent decades, becoming a public health problem (1).

Their prognosis improves if diagnosed and treated in early stages (2). Survival depends mainly on the extent of the disease: if the disease is localized (stage I), the 5-year survival is 90%, whereas if the disease is disseminated (stage IV) at the time of diagnosis the 5-year survival is 10% (2). Correct staging is essential to appropriate therapy and therefore provide improved survival (3).

Among imaging methods available is PET/CT (Positron Emission Tomography / Computed Tomography), a hybrid technique that combines nuclear medicine functional characteristics (PET) with morphologic features (CT).

PET/CT has proven useful in the detection of distant metastases, with a sensitivity of 87% and a PPV (positive predictive value) of 90% (4). The use of PET / CT may show unexpected results in up to 15 % of patients studied, including the detection of distant metastases, findings that change clinical management (4).

Objective:

The objective of this study was to describe the characteristics of patients referred for cutaneous melanoma and metastatic melanoma of unknown primary, evaluate metastatic sites and association between the presence of metastases to the location and depth of the tumor (*Breslow-index)

*Breslow-index: The most important factor is the distance from the granular layer to the deepest part of the tumor in millimeters.
Methods and materials

Type of study:

A retrospective descriptive study, review of the database of PET / CT between March 2011 to May 2013 was performed.

Patients:

Cases of **18F-FDG PET/CT derived by the diagnosis of cutaneous melanoma and melanoma metastases of unknown primary, considering variables such as age, sex, reason for the study, characteristics of melanoma as location, pathology were selected if they were available as *Breslow-index and distant involvement.

** 18F-FDG : The 18-F-fluorodeoxyglucose is a glucose analog, where the fluorine molecule is converted to fluorine - 18, a positron emitting radioactive isotope.

* Breslow -index : The most important factor is the distance from the granular layer to the deepest part of the tumor in millimeters.

Equipment and protocol PET / CT:

All exams of PET / CT were performed on a Siemens Biograph MCT 64 channels with acquisition of CT for attenuation correction and localization, followed by metabolic imaging 3D acquisition for the same field.

The readings of the PET / CT was performed approximately 60 minutes after injection of 18F-FDG. Prior to dosing of 18F-FDG, capillary glucose was measured by hemoglucotest with cutoff value of 160 mg /dl to perform the exam.

An acquisition extending from the vertex of the skull to the feet, placing arms in the prone position, performed with intravenous contrast.

All patients were interviewed prior to the exam by our nurse or medical technologist.

Image Interpretation:

Visual analysis:
The images were interpreted by two experienced radiologists (with 10 and 8 years experience as radiologists and 2.5 years respectively PET / CT). Images were reported separately and sequentially.

Semi quantitative analysis:

The standardized uptake value (SUV) is more quantitative system used in PET to measure activity in an injury. It is a semi-quantitative method that normalizes 18F - FDG by the lesion, based on the injected dose and the patient’s weight. Considered as positive (high probability of malignancy), SUV max > 2.5 and negative (low probability of malignancy) or physiological uptake SUV max < 2.5.

Data analysis:

Recorded data were entered into a worksheet (Excel; Microsoft). Statistical analysis was performed using the software (SPSS Statistics). For comparison of continuous variables, the Student’s t-test was used, while the Chi-square and Fisher’s test, Mann-Whitney U test were used for nominal variables. P < 0.05 was considered to indicate a significant difference.

Ethics committee:

Approved by our Institutional Review Board and Ethics Committee.
Results

Characteristics of the study population:

Out of a total of 1510 PET / CT performed between March 2011 to May 2013, 105 exams (67 patients) were made with a diagnosis of cutaneous melanoma or metastatic melanoma of unknown primary (6.9%).

Of the 67 patients studied, the reasons for the study were: staging 52.2 % (n = 35), 29.8 % follow-up (n = 20), re-staging 10.4 % (n = 7) and melanoma study metastatic unknown primary 7.4 % (n = 5).

63% (n = 42) were males and 37% (n = 25) were female. The average age was 54.8 years (SD = 9.9 years), with 56.6 years (SD = 15.7) for men and 51.7 (SD = 13.7) years for women. There were no significant differences between age and gender.

Primary tumor:

The locations of the primary tumor were: dorsal region 38.8 % (n = 26), lower extremities 25.3 % (n = 17), head and neck 13.4% (n = 9 ) , upper extremities 7.4 % (n = 5 ) anterior thorax 7.4% ( n = 5) and 7.4% unknown ( n = 5).

The main locations for both men and women were the dorsal region 35.7 % (n = 15) and 44 % (n = 11), followed by the lower extremities 26.1 % (n = 11) and 24 % (n = 6) respectively. There were no significant differences between sex and location of the primary tumor. [Figure 1]
Data were available as the depth of the tumor in 73% (n = 49), the mean Breslow-index was 1180 mm (SD=1270 mm). There were 12% (n = 6) of patients with index greater than 4000 mm.

**Characterization of metastatic disease:**

Of the patients studied, 34% (n = 23) had metastases in PET / CT, of these 73.3% (n = 17) were men with a mean age of 56.6 (SD= 15.7) and 26% (n = 6) were women with an average age of 51.7% (SD= 13.7), there were no significant differences. 52.2% (n = 35) were patients in staging, 29.8% (n = 20) at follow-up, 10.4% (n = 7) re-staging and study of metastatic melanoma with unknown primary 74% (n = 5), there were no significant differences between these groups.

The sites of metastases from the general group in descending order were: lymph 86.9 % (n = 20), skin 34.7 % (n = 8), soft tissue (muscle-fascial planes) 30.4 % (n = 7), chest 30.4 % (n = 7), abdominal cavity 26.0% (n = 6), bone 21.7 % (n = 5), and other sites 13
There were no significant differences between gender and metastatic sites. 47.8 % (n = 11) had metastases in more than one location.

The lymphatic metastatic involvement was the most frequent 86.9 % (n = 20). Characterized by lymphadenopathy mostly distant to the primary tumor location, with SUV max between 2.7 to 27.8 and whose sizes vary from single lymph nodes of 0.9 x 0.6 cm to lymphadenopathy clusters of up to 22 x 12 cm. [Figure 2]

Fig. 2: 47 years old woman. Melanoma in the dorsal region; suspected recurrence. Image shows a hypermetabolic lymphadenopathy conglomerate in right axillary region. This invades the chest wall and muscles and extending to the supraclavicular fossa, with a diameter of 22 x 12 cm (SUV max 19.3).

References: - Santiago/CL

34.7 % (n = 8), cutaneous, subcutaneous nodular metastases, were observed with an SUV max between 3.2 to 31.1 and diameters ranged from 0.7 to 1.9 cm. [Figure 3]
**Fig. 3**: 60 years old man. Melanoma in the dorsal region; control study. Multiple metastatic skin lesions are observed also in muscular layers and nodules in the abdominal cavity.

**References**: Santiago/CL

30.4 % (n = 7) metastases were found in the soft tissues (muscle - fascial planes), characterized by muscle nodules between 0.5 to 6.5 cm in diameter and 22 SUV max [Figure 4]
Fig. 4: 31 years old man. Melanoma in the dorsal region; control study. Nodules were observed in muscular layers, some of these are not visible in CT

References: - Santiago/CL

Metastatic lung nodules were found in 30.4% (n = 7), of these 57.1% (n = 4) were positive PET SUV max to 17.1 and 1.9 cm diameter, the other 42.8% (n = 3) were too small to be characterized due to the low sensitivity of PET in nodules smaller than 1 cm. [Figure 5]

Fig. 5: 55 years old man. Melanoma in the dorsal region; control study. Single nodule in the upper lingular segment 2.3 (SUV max 13.9)

References: - Santiago/CL
Metastases were found in the abdominal cavity at 26.0 % (n = 6) of the patients were characterized by nodules in the liver parenchyma (n = 1) with a SUV max to 6.6 and 2.2 cm [Figure 6], nodule in the gallbladder (n = 1) with SUV max of 11.7 and 1.6 cm [Figure 7], nodules in the pancreas (n = 1) with SUV max of up to 23.6 and a maximum diameter of 1.4 cm [Figure 8], nodules in the adrenal glands (n = 2) with SUV max of 20.8 and a maximum diameter of 3 cm [Figure 9] and commitment in the peritoneum and retro-peritoneum (n = 3) with nodular clusters of SUV max to 17.6. [Figure 10]

**Fig. 6:** 70 years old man. Melanoma in pectoral region; control study. Image shows a hepatic lesion in segment VIII (2.2 cm, SUV max 6.53) and in segment V (1.7 cm, SUV max 4.42), the latter not visible on CT.

**References:** - Santiago/CL
Fig. 7: 79 years old man. Melanoma in right forearm; staging. Image shows a hypermetabolic nodule in the gallbladder (2.9 cm, SUV max 23.3).
References: - Santiago/CL

Fig. 8: 39 years old woman. Melanoma in dorsal region; control study. Image shows a hypermetabolic nodule in the head of pancreas (1.4 cm, SUV max. 27.4).
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Fig. 9: 59 years old man. Melanoma in dorsal region; control study. Image shows a right adrenal mass with necrotic component (arrowhead) and hypermetabolic neoplastic component (arrow) (SUV max 19.8)

References: - Santiago/CL
**Fig. 10:** 32 years old man. Metastatic melanoma of unknown primary. Image shows multiple nodules in the mesentery and retroperitoneum, the largest in the left lower quadrant (11 cm, SUV max. 21.3)

**References:** Santiago/CL

The bone metastases were 21.7 % (n = 5), showing lytic lesions and infiltration of the marrow cavity with SUV max to 13.2. [Figure 11]
Fig. 11: 59 years old man. Melanoma in dorsal region; control study. Image shows hypermetabolic bone lesions, into a vertebral body and the right sacral (3 cm, SUV max 13.2).

References: - Santiago/CL

Other sites of metastatic lesions were found in 13% (n = 3), these were located in the testis [Figure 12], the palatine tonsils [Figure 13] and the right atrium. [Figure 14]

Fig. 12: 79 years old man. Melanoma in right forearm; staging. Image shows a hypermetabolic nodule in right testicle (9 mm, SUV max of 7)

References: - Santiago/CL
Fig. 13: 40 years old man. Metastatic melanoma of unknown primary. Image shows a hypermetabolic area in the left amygdala (SUV max 11.8) that has no clear representation on CT.

References: - Santiago/CL

Fig. 14: 46 years old man. Melanoma on right leg; control study. Image shows node in the right atrium (1.4 cm, SUV max 15.9)

References: - Santiago/CL

18% of patients metastases were detected by PET, which would not have been detected by CT, such as lymphadenopathy not meeting morphological criteria of malignancy in
CT (for standard size) and other non-visible tumors in CT by being isodense site or surrounding parenchyma.

Were not considered brain metastases by the low sensitivity of PET / CT in detection given the high metabolic activity of the parenchyma.

A significant association between tumor location and the presence of metastasis was found more frequent in melanomas located in the dorsal region 56% (p <0.006)

There was significant association between tumor depth measurements with the Breslow index and the presence of metastases (p <0.04).

Outcome of patients in control:

Control patients were 14, with an average of 3.7 exams per patient. Of these 28.5% (n = 4) showed secondary involvement in staging and during follow-up, the remaining 71.4% of patients (n = 10) had secondary lesions in the staging and monitoring progression observed in 9 patients and remission in one patient whose metastasis was surgically removed. [Figure 15]
Fig. 15: 32 years old man. Metastatic melanoma of unknown primary. (A) Initial examination and (B) control at 8 months. Dramatic progression of metastatic disease, with increase in number and size of hypermetabolic nodules in the cervical region, mediastinum, retroperitoneum and skin.

References: - Santiago/CL

False positives:

Of the total 67 patients, 20.8% (n = 14), uptake was observed in inflammatory diseases such as thyroiditis, rotator cuff tendinopathy, degenerative disease and post surgical changes. [Figure 16] and [Figure 17]
Fig. 16: 85 years old man. Nuchal Melanoma in staging. The study shows no secondary metastatic involvement. Increased tracer uptake in shoulders, sternocleidomastoid muscle and sternoclavicular joints are in relation to degenerative pathology.

References:
- Santiago/CL
Fig. 17: 55 years old woman. Melanoma in cheek. The study shows no secondary metastatic involvement. The thyroid is enlarged and has a higher uptake of the tracer. An ultrasound was performed demonstrating the appearance of a chronic thyroiditis.

References: - Santiago/CL
Fig. 1

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Conclusion

Melanoma has quickly become a health problem in many countries, which is reflected in a dramatic increase in incidence between 3-7% (5) and mortality rate (3), one of the cancers that more has increased in recent years (5).

The alarming increase cancer, possibly due to many factors including the relationship with the increase of ultraviolet radiation, studies have estimated that this is responsible for 79% to 96% of melanoma cases (6).

Worldwide, the incidence is highest in Australia and New Zealand, with 30 to 60 cases per 100,000 population per year and ranks fourth in frequency in these countries (1-2).

It has been estimated that in 2013, 76,690 new cases will be diagnosed and approximately 9480 melanoma patients with melanoma die in the United States (7).

It is more common in Caucasians, between 35 and 65 years, the male / female ratio is 1.5/1, with a mean age at diagnosis of 57 years and a mean age of death of 67 years (8). In this study, a higher percentage of men affected in 63%, with an average age of 56.6.

Melanoma can appear anywhere on the body, in men usually affects the trunk, head or neck, and in women most commonly develops in the arms and legs (9). In this study a high incidence of melanomas of dorsal location and top tips for both men and women, similar to that described in the literature (5).

Melanoma can spread through the blood, by lymphatic channels, along the vascular channels or by direct local invasion. Metastatic disease can occur anywhere in the body, being the path and unpredictable pattern of spread (10).

The prognosis of patients with melanoma is determined by histological type and the presence and extent of metastatic disease (10).

The evaluation of macroscopic metastases PET / CT has a sensitivity of 87% and PPV to 90% (4), however, the PET / CT is limited in early stage patients without lymph node metastases, biopsy of sentinel node being much more sensitive in detecting microscopic lymph node metastases (4).
PET / CT is more sensitive than other anatomical imaging techniques such as CT or MRI. The sensitivity is higher (# 90%), when metastases are larger than 1 cm diameter, however tumor implants under 0.6 cm can also be recognized when background activity is low, such as the lung parenchyma (4).

PET CT can also identify metastases that go unnoticed in CT to have densities similar to its background, such as some liver and muscle metastases (4) PET / CT has proven to be the best method in the diagnosis of bone metastases (10)

Metastases are more frequent in lymph nodes 60-80 %, skin and subcutaneous tissue 50 %, non- visceral sites that visceral sites (11). Although virtually any organ can be involved, the most common visceral metastatic sites reported in clinical trials are the lung (14-20 %) , liver (14-20 %) , brain (12 -20 %) , bone (11 -17%) , and intestine ( 1 -7%), while metastases elsewhere are less common ( 11).

As described in the literature the main sites of metastases were found lymph nodes, skin and soft tissue (not visceral sites) . The most frequent visceral metastases were lung nodules and metastasis in abdominal organs and retroperitoneum. Unusual sites of metastasis was the atrium, testicles and tonsils . Brain metastases were not evaluated due to physiologic FDG uptake by the brain (12 )

The PET / CT showed utility in assessment of progression and regression of disease in patients who had more than one control.

Tumor thickness measured in Breslow-index is one of the main factors that determines treatment and prognosis (11), when the Breslow-index is less than 1.5mm survival at 5 years is 93% and 97%, while more than 3.5 mm index is 47% and 55% in men and women respectively (12).

Turn the Breslow-index is the main risk factor for lymph node metastasis, the incidence of metastasis is directly correlated with tumor thickness being 1% for minor injuries at 0.75mm, 8.3% in lesions between 0.76 to 1.5 mm, 22.7% for lesions between 1.51 to 4.0 mm and 35.5% in lesions greater than 4mm (13)

In this study a significant association between the presence of metastatic disease and increased Breslow depth was found.

A significant association between melanomas dorsal location and the development of metastases, similar to the data described in the literature.
False-positive PET / CT, correspond to inflammatory changes (recent surgeries, infections, granulomatous diseases) and physiological uptake by muscles, brown fat, myocardium, bowel loops and renal collecting system. (14)

Some of the limitations of PET / CT are the high radiation dose and it is not a widely available method and its low sensitivity in early stages (10)

It remains to study other associated prognostic factors and evaluate disease control and potential utility SUV.
Personal information

Javiera Valentina Aguirre Fernández, MD
Radiology Resident. Facultad de Medicina Clínica Alemana - Universidad del Desarrollo. Santiago, Chile. javiera.aguirre.fe@gmail.com

Giancarlo Schiappacasse Faundes
Assistant Professor of Radiology. Facultad de Medicina Clínica Alemana - Universidad del Desarrollo. Santiago, Chile.

Claudio Silva Fuentealba
Assistant Professor of Radiology. Facultad de Medicina Clínica Alemana - Universidad del Desarrollo. Santiago, Chile.


