Available online at www.sciencedirect.com
ScienceDirect
EJSO 37 (2011) 225–232
EJSO the Journal of Cancer Surgery
www.ejso.com

The value of pre operative S-100B and SUV in clinically stage III melanoma patients undergoing therapeutic lymph node dissection

S. Kruijff [a], E. Bastiaannet [a], M.J. Speijers [a], A.C.M. Kobold [b], A.H. Brouwers [c], H.J. Hoekstra [a,*]

[a] Surgical Oncology, University Medical Centre Groningen, University of Groningen, The Netherlands
[b] Laboratory Medicine, University Medical Centre Groningen, University of Groningen, The Netherlands
[c] Nuclear Medicine and Molecular Imaging, University Medical Centre Groningen, University of Groningen, The Netherlands

Accepted 14 December 2010
Available online 31 January 2011

Abstract

Introduction: High preoperative serum S-100B values and Standardized Uptake Values (SUV) of Fluorodeoxyglucose (FDG) in PET for clinically stage III melanoma patients could be indicators of recurrence after surgical treatment. Aim was to assess the correlation and the prognostic value of these markers.
Methods: All melanoma patients with palpable nodal metastases, without distant metastases, were included from February 2004 to December 2007. Preoperative SUV and S-100B was determined. The correlation between SUV and S-100B and their relations with DFS and DSS were calculated by Cox Proportional Hazard Analysis.
Results: 62 Patients, median age 56.9 years, were included in the study. An elevated S-100B was found in 31 patients (50%) and elevated SUV in 24 patients (38.7%). No relation was found between S-100B and SUV. DFS was reduced (31.1%) for patients with an elevated S-100B ($HR = 3.1$; $p = 0.02$) in comparison to a normal S-100B (44.6%). The DFS was 42.0% for patients with a SUV below the cut-off point and 29.0% for patients with an elevated SUV ($HR = 1.1$; $p = 0.8$). DSS was 60.7% in a normal S-100B and 44.7% for patients with an elevated S-100B ($HR = 2.2$; $p = 0.07$). DSS was 59.1% for patients with a normal SUV and 43.5% for patients with elevated SUV ($HR = 1.1$; $p = 0.8$).
Conclusion: S-100B and SUV in stage III melanoma are not correlated and each have different associations with various histopathological factors. S-100B, in contrast with SUV, is associated with nodal tumor load, and when elevated, predicts a shorter DFS.
Synopsis: Preoperative serum S-100B and Fluorodeoxyglucose (FDG) Standardized Uptake Value (SUV) in clinically stage III melanoma are not correlated. S-100B is a strong predictor for Disease Free Survival (DFS) in stage III melanoma.

Keywords: S-100B; SUV; Melanoma; Survival; TLND

Introduction

Melanoma causes more than 75% of all deaths related to skin cancer and its incidence has increased dramatically worldwide, especially in Caucasian populations.[1] During the period 1998–2007 the Dutch incidence increased from 13.2 to 20.0 newly diagnosed melanoma patients per 100 000 inhabitants.[2] The past 12 years, melanoma incidence rates have increased rapidly and are expected to keep on rising in the future. The absolute total number of new cases in the Netherlands is estimated to be well over 4800 in 2015, compared to approximately 2400 cases in 2000.[3]

Despite being diagnosed in an earlier phase of disease, which may be a result of increased awareness and better surveillance, melanoma patients presenting with palpable nodal metastases today still have a poor 5-year survival of 59% and 40% for stage IIIB and IIIC respectively.[4] Staging studies with whole-body FDG-PET and/or spiral CT in patients with stage IIIB melanoma have shown that about 27% of patients are upstaged and treatment was changed

* Corresponding author. Division of Surgical Oncology, University Medical Centre Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 (0)50 361 23 17; fax: +31 (0)50 361 48 73.
E-mail address: h.j.hoekstra@chir.umcg.nl (H.J. Hoekstra).

0748-7983/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejso.2010.12.013

for one of five patients.[5] Recently Balch et al. analyzed 2313 patients with AJCC stage III disease and for the complete cohort 5-year overall survival was 63%. However, when focusing on more specific patient groups, a tremendous heterogeneity in 5-year survival rates was observed (23%–87% 5-year survival).[6]

More than 60 years ago, Hill published about increased Lactate Dehydrogenase (LDH) as a prognostic serum marker in melanoma patients.[7] The last decades various biomarkers besides LDH have been studied, such as Melanoma Inhibitory Activity (MIA), S-100B and Standardized Uptake Value (SUV) in FDG-PET.[8,9] Weighing the evidence, LDH has high specificity for melanoma and literature demonstrates this marker to be elevated in advanced disease, predominantly in case of dissemination to the liver. However, today the most extensively studied melanoma biomarker is S-100B. This 21 kDa protein was first isolated from the central nervous system in vertebrates.[10] A preoperatively elevated serum S-100B in FDG-PET and CT evaluated patients with palpable nodal metastases is associated with a significantly worse survival.[10–13] Another prognostic marker was studied by assessment of the degree of Fluorodeoxyglucose (FDG) accumulation during Positron Emission Tomography in a melanoma metastasis; the Standardized Uptake Value (SUV).[14] Bastiaannet et al. proved that the uptake of FDG in the lymph node metastases in melanoma patients with clinical stage III melanoma is of prognostic value.[15]

High values of S-100B and FDG Standardized Uptake Value (FDG-SUV) measured preoperatively in stage III melanoma patients could both be highly specific indicators of early recurrence after surgical treatment. Possibly, S-100B values and FDG-SUV form a measurable reflection of the presence of a subclinical process of dissemination. Therefore, the aim of this study was to assess the correlation between both markers and to study their association with Disease Free Survival (DFS) and Disease Specific Survival (DSS).

Material and methods

Patients

Melanoma patients, previously staged as AJCC I or II, now presenting with palpable and pathologically proven lymph node metastases (AJCC stage IIIB or IIIC) were prospectively included in this study from February 2004 to December 2007. Patients were staged with whole-body FDG-PET and spiral CT. In case of negative test results for distant metastases, patients were eligible for therapeutic lymph node dissection (TLND) and were included in this study. Sentinel lymph node positive patients were excluded from this study. Patients received adjuvant radiotherapy (20×2.4 Gy) in case of a nodal metastasis of $\geq$3 cm in diameter, $\geq$3 tumor positive lymph nodes or the presence of extranodal growth.[16,17]

Patient characteristics and follow up

Age, sex, treatment strategy of primary melanoma, date of primary melanoma diagnosis, characteristics of the primary melanoma (Breslow thickness, localization, ulceration status, Clark level) and characteristics of the lymph node metastases (localization, number of lymph nodes removed, number of tumor positive nodes, presence of extranodal growth, lymph node size and AJCC stage III B/C) were recorded, as well as the date of recurrence or death. Any form of melanoma recurrence after TLND was scored as recurrent disease.

Follow-up strategy was the same for all patients. Three monthly history and physical examination in the first year after TLND, 4 monthly in year 2, 6 monthly in years 3–5 and annual visits and chest radiographs for the subsequent five years.

PET protocol

FDG-PET and CT were performed preoperatively in a random order. FDG was produced on site.[18] Before FDG injection, patients were instructed to fast for at least 6 h and drink 1 L of water. After intravenous injection of FDG (Range 220–690 MBq), whole-body PET-imaging was performed; two/three dimensional mode, emission scans 5 min per bed position, starting 90 min after injection of FDG. Patients were scanned from scalp to feet, using a Siemens ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN). FDG-PET readings were performed by attending staff nuclear medicine physicians.

CT protocol

In the CT protocol a 64-slice spiral CT (Siemens Somatom Sensation) was performed of neck, chest and abdomen. Before starting the procedure oral (800 ml) and intravenous contrast agents were administered to the patient using standard imaging protocols. CT images were interpreted by attending staff radiologists.

Standardized Uptake Value (SUV)

The SUV depends on the amount of injected radioactivity, the patient's weight and the calibration factor of the camera. The value is calculated according to the following formula: SUV mean = radioactivity concentration in tissue (Bq/Kg)/(injected dose [Bq]/patient weight [Kg]). Three dimensional regions of interest were placed semi-automatically over the tumor on multiple slices using a software program and a threshold of 70% of the maximum pixel value within the tumor. In case of multiple metastases in the lymph node basin, the lesion with the most intense uptake was analyzed. For SUV the median of 8.4 was used as cut-off value in absence of a standardized cut-off value. Currently no cut-off point is described in literature although initiatives have been undertaken to create a new protocol using standardized uptake values.[19]