Author's response to reviews

Title: Sentinel lymph node biopsy in melanoma: Our 8-year clinical experience in a single French institute (2002-2009)

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Author's response to reviews: see over
To the Editorial Office of the BMC Dermatology Journal

Dear Sir,

We are pleased to note that the reviewers of our manuscript MS: 1698886129771208 entitled “Sentinel lymph node biopsy in melanoma: Our 10-year clinical experience in a single French institute (2002-2009)” by Caroline Biver-Dalle et al, that we submitted for publication in the BMC Dermatology suggested minor revisions which were easily addressed.

We enclose herewith the specific answers to the reviewers. Please find attached the revised underlined and highlighted manuscript. We hope that the editorial board will now find our manuscript of interest for the readers of the BMC Dermatology.

Yours faithfully,

Prof. François Aubin

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Answers to specific comments

Editorial points:

1. Ethical Approval
In the case of studies that have been exempted from review, we require an explicit statement at the end of the Methods section stating that the study has been submitted to a legally constituted ethics committee and deemed exempt from review and giving the name and study reference of the committee. If this process has not been conducted by an ethics committee, then we require a copy of the letter detailing the permissions; depending on the provenance of the letter, we may need to ask for further clarification. If we judge that the author of the letter did not appropriately fulfil the role of an ethics committee, then we will require the author to submit the study to a legally constituted ethics committee. In such cases, we will not take any further decisions until either the study is approved or deemed exempt from review.

Our retrospective study based on database was not eligible for the submission of our research ethics committee. By definition, the Cancer registry has the authorization from the Privacy and Data Protection National Agency (authorization CNIL numéro 903417) to conduct studies based on its own database. Patients were selected and each clinical file obtained from the Cancer Registry was re-examined and the following data were collected: epidemiological criteria (sex, age), histological criteria, clinical features, SLN status (positive or negative), results of CLND and evolution criteria (relapse and survival). The epidemiological and histological data were collected from the Cancer Registry, whereas the evolution criteria were gathered from the hospital clinical files or by writing to family practitioners. We added a comment on page 4, lines 11-19.

2. Tables
Tables should be included in the main manuscript document and should appear after the Figure Legends section. Can you please remove Tables 1 and 2 from the additional files.
Ok, done.

3. General Formatting
You now have an opportunity to ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.
OK
Reviewer: ali cadili

- The authors mention that vital blue dye was used in only 9 patients; they also mention, elsewhere, that 6 patients failed the SLN procedure. Did any of those 6 patients have the vital blue dye used on them for the SLN procedure?

No, the 6 patients who failed the SLN procedure were not investigated with the vital blue dye (see comment on page 7, lines 6-7).

- Can the authors offer any insight as to how the vital blue dye was used so infrequently (was this merely surgeon preference)?

Yes, our surgeons prefer to not use the blue dye for the SLN procedure.

- The 2nd sentence in the "Surgical and adjuvant therapy" section on page 5 should be re-written so as to remove any ambiguity. I believe the guidelines state that interferon should be offered to two groups of patients: 1) patients with a primary that is equal to or greater than 1.5 mm thickness PLUS positive nodes, 2) high risk primary tumours (even with negative nodes)

We modified this sentence as follows (page 5, lines 22-26): "According to French guidelines, all patients with primary CM larger than or equal to 1.5 mm in thickness as well as patients with positive SLN and positive CLND and patients with high-risk primary melanoma (tumor thickness > 4 mm and ulceration) were considered for adjuvant interferon alpha therapy, low-doses and high doses of interferon, respectively."

- The authors state that in 67% of cases only one SLN was harvested; the authors should expand on the acceptable maximal number of SLNs that can be harvested during this procedure as well as the criteria they used intraoperatively for deciding on the number of nodes they choose to harvest; other larger series have reported a higher number of SLNs typical harvested during this procedure.

Although only one SLN was harvested in 67% of cases, the mean number of SLN harvested was 1.5 +/- 1 in our study, very similar to those found by previous studies (Gershenwald et al, 1999: 1.5; Testori et al, 2009: 1.7). Furthermore, Gershenwald et al (J Clin Oncol 2008) found that among the 343 patients who underwent CLND, the majority (72%) had only one positive SLN as compared to 67% in our study. To our knowledge, there are neither consensus nor recommendations on the minimal or maximal number of SLN that should be harvested during the procedure. We added this comment on page 9, lines 25-26 and 10, lines 1-5.

It should also be kept in mind that this procedure was introduced with the objective to identify the SLN and not to replace a systematic prophylactic LND, which has already demonstrated its lack of benefit for the patient. It is our opinion that the interpretation of studies which reported a higher number of SLN (up to 12 !) should be thus questioned.

The SLN was identified intra-operatively using a gamma probe. After SLN harvesting, the radioactive count was measured ex vivo using the gamma probe. Echelon nodes were then harvested if they had a count ≥ 10% of the SLN. The background count of the lymph node basin was then measured to ensure that no further radioactive nodes remained. We added this comment on page 5, lines 2-7.
The authors state that only 95% of patients proceeded to additional dissection after a positive SLN result. Given that most guidelines recommend additional dissection, the authors should mention the reasons those 5% did not get further surgery (ex: types of medical comorbidities, refused consent). Also, did the authors' follow up data reveal that those 5% had any higher recurrence rates than the 95% of patients that did receive additional surgery?

One patient had a popliteal positive SLN and refused further surgical intervention and one patient had contraindications for radical lymphadenectomy. None of them relapsed.

We added this comment on page 7 line 26 and page 8, lines 1-2.

An inclusion of the number and types of complications of completion lymph node dissection (following SLN biopsy) would greatly enhance the paper.

Post-operative complications of additional CLND were observed in 14% of patients (6/42), including lymphedema (3), hematoma (1) and neuropathic pain (1) and complex regional pain syndrome (1). We added this comment on page 9, lines 15-17.

The authors need to expand on the various attempts made by others to define specifically which SLN-positive patients are more likely to benefit from additional nodal dissection. They did briefly allude to this in the Discussion section but a further discussion and inclusion of the following references MUST be carried out and would greatly enhance the manuscript: Total sentinel lymph node tumor size predicts nonsentinel node metastasis and survival in patients with melanoma. Cadili A, Scolyer RA, Brown PT, Dabbs K, Thompson JF. Ann Surg Oncol. 2010 Nov;17(11):3015-20


We agree with this comment and we added the following modification on page 12, lines 12-26 and page 13, lines 1-2:

“Many attempts have been made to predict non-SLN (NSLN) metastasis based on demographic, primary tumor, and SN features of patients with melanoma. Previous studies (Gershenwald 2008, Cadili 2010) indicate that overall SLN tumor burden, primary tumor thickness, and number of SLN harvested may be useful in identifying a group at low risk for positive NSLN. However, marked variability in the correlation of individual features with NSLN metastases and the degree of this correlation has characterized the literature on this issue to date (Scolyer 2004, Debarbieux 2007). There is currently no consensus regarding what degree of risk of NSLN involvement indicates that it is safe to forego CLND. Before elimination of CLND can be advocated, prospective clinical trials designed to assess the safety of omitting formal CLND with respect to survival and locoregional control in low-risk groups are needed. The ongoing Multicenter Selective Lymphadenectomy Trial II (Morton 2004) which compares CLND versus close observation with sonography and clinical examination for patients with a positive SLN, should provide valuable information about which patients might be spared a CLND.”
Reviewer: Roberto Cecchi

I have read the article by Biver-Dalle C et al, that deals with the use of lymphatic mapping/sentinel lymph node biopsy (SLNB) in patients with melanomas. Several studies on this topic have been done previously, and with larger patient populations, so the paper lacks some significance. However, the manuscript reports a single-centre experience and further support the conclusions of many other authors, regarding the role of SLNB in melanomas. The paper is well-written and all sections (introduction, patients and methods, discussion) appear well structured. English is generally correct. However, I suggest to better revise the recent literature regarding French studies on SLNB in melanoma. I found several articles reporting the experiences of French departments/institutions on this topic. In particular, the article by Lourari S, Paul C, Gouraud PA, et al. Sentinel lymph node biopsy for melanoma is becoming a consensus: a national survey of French centres involved in melanoma care in 2008. J Eur Acad Dermatol Venereol. 2011 Sep 20. doi: 10.1111/j.1468-3083.2011.04267.x. [Epub ahead of print] should be cited and briefly discussed.

As suggested, we briefly discussed this paper in the introduction, page 3, lines 2-4. However, this study only evaluated the practice of SLN biopsy for melanoma in France but did not report the results of this procedure.