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The number of excised lymph nodes is associated with survival of melanoma patients with lymph node metastasis

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Abstract

Background Although the number of excised LNs has been associated with patient prognosis in many solid tumors, this association has not been widely investigated in cutaneous melanoma. This study aims to evaluate the association between the number of excised regional lymph nodes (LNs) and melanoma-specific survival.

Patient and methods Clinico-pathological data from 2507 patients with LN metastasis treated at nine Italian centers were retrospectively collected.

Results The number of excised LNs correlated with younger age ($P < 0.001$), male sex ($P < 0.001$), neck LN field ($P < 0.001$), LN micrometastasis ($P < 0.001$) and number of positive LNs ($P < 0.001$).

The number of excised LNs was an independent prognostic factor (HR = 0.85; $P = 0.002$) after adjustment for other staging features. Upon subgroup analysis, the number of excised LNs had a significant prognostic value in patients bearing 1.01–2.00 mm (HR = 0.79; $P = 0.032$) and 2.01–4.00 mm (HR = 0.71; $P < 0.001$) thick melanomas, primary tumors showing ulceration (HR = 0.86; $P = 0.033$) and Clark level V of invasion (HR = 0.86; $P = 0.010$), LN micrometastasis (HR = 0.83; $P = 0.014$) and two to three positive LNs (HR = 0.71; $P = 0.001$). Finally, this study investigated the influence of the number of excised LNs on patient staging: only when ≥11 nodes were excised the AJCC N stage could stratify prognosis ($P < 0.001$). Considering the number of excised LNs for each lymphatic field, at least 14, 11, 10 and 12 LNs were needed to stage patients according to the AJCC N stage after a lymphadenectomy of the neck, axilla, inguinal and ilioinguinal LN fields, respectively.

Conclusions The number of excised LNs can be considered for risk stratification of patients with regional LN metastasis from cutaneous melanoma. We demonstrated that a minimum number of LNs is required for the correct staging of patients. Further research is needed to evaluate the effectiveness of the minimum number of LNs to be dissected.

introduction

The number of positive lymph nodes (LNs) is one of the main determinants of prognosis in melanoma patients with LN metastasis, along with the LN tumor burden (i.e. micro- or macrometastasis) and the presence of ulceration in the primary tumor [1]. Based on the fact that patients with advanced LN disease are at greater risk of disease progression, randomized trials have investigated whether lymphadenectomy may be effective in patients with clinically negative regional LN [2]. Although these trials were negative [2, 3], analyses of nonrandomized participants revealed that dissection offered a survival benefit in case of subclinical LN metastasis (i.e. LN metastasis detected with sentinel LN biopsy, SLNB) [3, 4], leading to the design of the ongoing Multicenter Selective Lymphadenectomy Trial-II (MSLT-II), which is comparing lymphadenectomy and observation in SLNB-positive patients [5]. This trial is expected to answer the question on the therapeutic role of lymphadenectomy carried out for subclinical LN metastasis, but results will take years to be mature for analysis. In the meanwhile, investigating whether the number of excised LNs at lymphadenectomy is associated with patients' outcome can provide useful information for the management of patients with skin melanoma. Studies so far conducted demonstrated the prognostic value of the LN ratio, which is the proportion of positive among examined LNs [6–11], supporting, though indirectly, the number of excised LNs as a prognostic factor. However, these findings can be biased by the

inclusion of the number of positive LNs, one of the major determinant of melanoma patient prognosis, in the LN ratio [12]. Our objective was to investigate the association between the number of excised LNs and melanoma-specific survival in a large cohort of patients with metastatic regional LNs.

patients and methods

Retrospective data from melanoma patients with LN metastasis who underwent a lymphadenectomy (1993–2011) at nine IMI centers were gathered in a multicenter dedicated database.

Data were extracted according to the following selection criteria: (1) LN metastasis from known single primary melanoma; (2) absence of in-transit and distant metastasis at the time of primary melanoma diagnosis and lymphadenectomy; (3) lymphadenectomy of a single regional field (neck, axillary or groin); (4) availability of information regarding tumor thickness, LN tumor burden, number of excised and positive LNs (including SLNB or any other LN biopsy when carried out) and melanoma-specific survival. Patients who had a popliteal, an epitroclear and a pelvic only LN dissection were excluded, as well as patients who underwent a lymphadenectomy for regional LN failure after a previous dissection. Conversely, this series included SLNB-negative patients who have had a regional LN recurrence without distant disease and underwent a lymphadenectomy.

Description of surgery technique, pathology protocol and statistical method is available as online available supplementary material.

results

There were 2507 patients eligible for this study. Clinicopathological features and distribution of the number of excised LNs are reported in Tables 1 and 2, respectively.

Table 1. Clinical and tumor characteristics of 2507 patients who underwent lymph node (LN) dissection for melanoma LN metastasis

Variables		**No.**	**%**
Age	Years	Median: 54 (IQR 42–66)	
Sex	Male	1385	44.7
	Female	1122	55.2
AJCC T stage	T1 (≤1 mm)	232	9.2
	T2 (1.01–2 mm)	604	24.1
	T3 (2.01–4 mm)	914	36.5
	T4 (>4.00 mm)	757	30.2
Ulceration	Absent	1273	50.8
	Present	1233	49.1
Clark level of invasion	II–IV	2,261	90.2
	V	246	9.8
LN field	Axilla	1154	46.0
	Groin	1142	45.6
	Neck	211	8.4
Clinical scenario	Immediate completion lymphadenectomy[a]	1688	67.3
	Delayed completion lymphadenectomy[b]	275	11.0
	Delayed therapeutic lymphadenectomy[c]	301	12.0
	Immediate therapeutic lymphadenectomy[d]	243	9.7
LN tumor burden	Micrometastasis (SLNB-positive)	1688	67.4
	Macrometastasis (clinically positive LNs)	819	32.6
AJCC N-stage category	N1a (1 positive LN—micrometastasis)	1112	44.4

Variables		No.	%
	N1b (1 positive LN—macrometastasis)	314	12.5
	N2a (2–3 positive LNs—micrometastasis)	415	16.6
	N2b (2–3 positive LNs—macrometastasis)	239	9.5
	N3 (≥4 positive nodes)	427	17.0

Clinical scenario is described as per Spillane et al. [21] as follows. [a]SLNB-positive patients who undergo immediate completion lymphadenectomy. [b]SLNB-negative patients who undergo a delayed completion lymphadenectomy for regional LN recurrence. [c]Patients with clinically negative LN and no SLNB at the time of primary melanoma diagnosis that later develop regional LN failure and have delayed therapeutic lymphadenectomy. [d]Patients with regional LN disease at the time of primary melanoma diagnosis and have immediate therapeutic lymphadenectomy. CI, confidence interval; IQR, interquartile range; SLNB, sentinel LN biopsy.

Table 2. Distribution of the number of excised lymph nodes (LN) according to the dissected lymph node field

LN field	Axilla	Neck	Groin inguinal	Groin ilioinguinal	Overall
No. of cases	1154	211	208	944	1507
Mean no. of excised LNs (95%CI)	22 (21–22)	28 (26–31)	12 (11–13)	22 (21–22)	21 (21–22)
Median no. of excised LNs (IQR)	20 (15–27)	26 (17–38)	11 (9–14)	21 (16–26)	15 (20–27)

CI, confidence interval; IQR, interquartile range.

Upon multivariable regression analysis, later years of diagnosis (difference between median values: three LNs; $P < 0.001$), younger age (difference between median values: two LNs; $P < 0.001$), male sex (difference between median values: two LNs, $P = 0.004$), neck LN field ($P < 0.001$, Table 2), micrometastasis (difference between median values: one LN; $P < 0.001$) and a greater number of positive LNs ($P < 0.001$, Table 2) were associated with a greater number of excised LNs, while groin LN field ($P < 0.001$, Table 2) correlated with lesser excised LNs (supplementary Table S1, available at *Annals of Oncology* online).

At a median follow-up of 54 months [interquartile range (IQR) 21–98], 623 patients (25%) died for melanoma. The number of excised LNs was an independent predictor of melanoma-specific survival after adjustment in a multivariable model which encompassed also later year of diagnosis, older age, male sex, primary tumor showing greater thickness, ulceration and Clark level V, as well as AJCC sub-stages N2 and N3 (Table 3). The enrolling center and the LN tumor burden showed prognostic value at univariate analysis but were no longer statistically significant when adjusted at multivariable analysis.

Table 3. Clinicopathological variables associated with melanoma-specific survival: results of the univariate and multivariable Cox regression analysis

Variables		Univariate analysis				Multivariate analysis			
		HR	95% CI		*P*-value	HR	95% CI		*P*-value
Year of diagnosis	1993–2001	1				1			
	2002–2011	0.75	0.63	0.98	*<0.001*	0.73	0.61	0.88	*0.001*
Enrolling center	<200 patients	1				1			
	≥200 patients	0.81	0.67	0.98	*0.035*	0.86	0.71	1.05	*0.118*
Age	Years	1.016	1.01	1.02	*<0.001*	1.011	1.006	1.017	*<0.001*
Sex	Female	1				1			
	Male	1.51	1.29	1.78	*<0.001*	1.48	1.24	1.77	*<0.001*
Breslow thickness	mm	1.03	1.02	1.04	*<0.001*	1.03	1.02	1.04	*0.003*
Ulceration	Absent	1				1			
	Present	1.73	1.47	2.03	*<0.001*	1.60	1.35	2.31	*<0.001*
Clark level of invasion	II–IV	1				1			
	V	2.10	1.66	2.64	*<0.001*	1.79	1.39	2.31	*<0.001*

Variables		Univariate analysis				Multivariate analysis			
		HR	**95% CI**		***P*-value**	**HR**	**95% CI**		***P*-value**
LN field	Axilla	1				1			
	Groin	0.89	0.75	1.05	*0.161*	0.79	0.74	1.07	*0.316*
	Neck	1.19	0.90	1.57	*0.232*	1.09	0.80	1.49	*0.235*
LN tumor burden	Macrometastasis	1				1			
	Micrometastasis	0.73	0.62	0.86	*<0.001*	0.87	0.72	1.04	*0.133*
AJCC N sub-stage	N1 (1 pos LN)	1				1			
	N2 (2–3 pos LNs)	1.53	1.28	1.85	*<0.001*	1.31	1.07	1.60	*0.008*
	N3 (≥4 pos LNs)	2.01	1.65	2.45	*<0.001*	1.62	1.30	2.02	*<0.001*
No. of excised LNs		0.90	0.82	0.99	*0.028*	0.85	0.76	0.94	*0.002*

HR, hazard ratio; CI, confidence interval; LN, lymph node.

Multivariable survival analysis was conducted within patient subgroups to assess whether the number of excised LNs is significantly associated with survival in specific tumor substages (Table 4). The number of excised LNs was a prognostic factor in patients who had an intermediate thick primary, tumors showing ulceration and Clark level V, micrometastasis and two to three positive LNs.

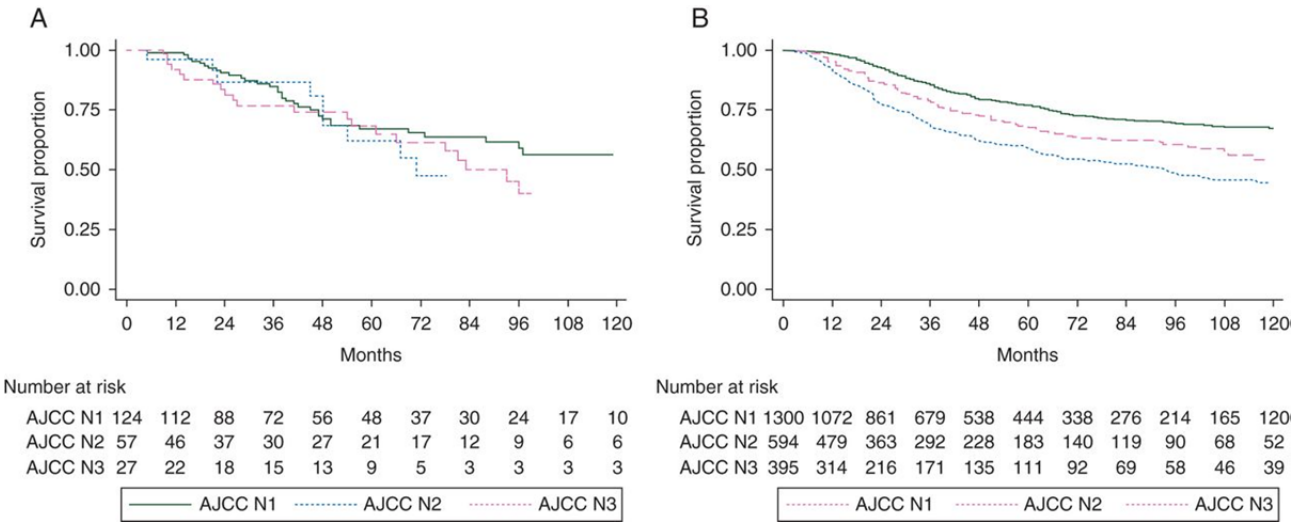
Table 4. Association between the number of excised lymph nodes (LNs) and melanoma-specific survival in patient subgroups at multivariable Cox survival analyses

Subgroup		HR	95% CI		*P*-value
AJCC T stage	T1 (≤1 mm)	1.45	0.83	2.54	*0.194*
	T2 (1.01–2.00 mm)	0.79	0.64	0.98	*0.032*
	T2–T3 (2.01–4 mm)	0.71	0.59	0.85	*<0.001*
	T4 (>4.00 mm)	1.02	0.86	1.22	*0.805*
Ulceration	Absent	0.88	0.76	1.02	*0.095*
	Present	0.86	0.74	0.99	*0.033*
Clark level of invasion	II–IV	0.83	0.69	1.00	*0.058*
	V	0.86	0.77	0.96	*0.010*
LN tumor burden	Micrometastasis	0.83	0.72	0.95	*0.014*
	Macrometastasis	0.90	0.77	1.04	*0.156*
AJCC N substage	N1 (1 positive LN)	1.45	0.83	2.54	*0.194*
	N2 (2–3 positive LNs)	0.73	0.64	0.91	*0.003*
	N3 (≥4 positive LNs)	1.00	0.81	1.23	*0.967*

Hazard ratio (HR) and confidence interval (CI) refer to the prognostic value of the number of excised LNs. Each multivariate model includes the number of excised LNs along with the following covariates: year of diagnosis, enrolling center, age, sex, tumor thickness, ulceration, Clark level of invasion, LN tumor burden, AJCC N stage.

In order to prove that the number of excised LNs influences tumor staging, we searched for a cutoff value that identifies a number of excised LNs that may be required for staging patients with LN metastasis. The role of the number of excised LNs in providing better tumor staging is visualized in Figure 1: patients with ≤10 excised nodes (*N* = 208, 8.3%) were not adequately staged as showed by the crossing survival curves of the AJCC N-stage 1, 2 and 3 (test for trend, *P* = 0.406; Figure 1A). This lack of prognostic stratification was maintained at multivariable analysis after adjusting for the other considered variables [AJCC N2 versus N1, HR = 1.62; 95% confidence interval (CI) 0.88–2.98, *P* = 0.118; AJCC N3 versus N1, HR = 0.82; 95% CI 0.33–2.04, *P* = 0.673]. Differently, when ≥11 nodes were yielded (2299, 91.7%), patients' prognosis can be properly stratified (test for trend, *P* < 0.001; Figure 1B). This prognostic significance was maintained at multivariable analysis after adjusting for the other considered variables (AJCC N2 versus N1, HR = 1.26; 95% CI 1.02–1.56, *P* = 0.034; AJCC N3 versus N1, HR = 1.67; 95% CI 1.33–2.11, *P* < 0.001).

Figure 1.



This panel depicts the prognostic discrimination of the AJCC TNM N substages (N1, 1 positive lymph node; N2, two to three positive lymph nodes; N3, ≥4 positive lymph nodes) according to the minimum number of 11 excised lymph nodes in all the patients (A and B). The left and the right figures report the survival of the AJCC N substages considering a lymph node count <11 and ≥11, respectively.

We searched for cutoff values for neck, axillary, inguinal and ilioinguinal LN fields (supplementary Figure S1, available at *Annals of Oncology* online). When less than 14, 11, 9 and 12 LNs were excised in the neck (P = 0.309), axilla (P = 0.957), inguinal (P = 0.880) and ilioinguinal (P = 0.404) lymphatic fields, respectively, the AJCC N substages did not have prognostic value. Strikingly, the AJCC N substage stratified patient survival when at least 14, 11, 10 and 12 LNs were excised in the neck (P = 0.05), axilla (P < 0.001), inguinal (P = 0.027) and ilioinguinal (P < 0.001) lymphatic fields, respectively.

Finally, we compared the prognostic value of inguinal and ilioinguinal lymphadenectomy. Multivariable analysis did not identify differences between patients who underwent these two dissections (HR 0.86; 95% CI 0.751–1.404; P = 0.17).

discussion

In this multicentric study, patients who had a higher number of excised LNs after lymphadenectomy showed a better prognosis, independently of clinical features and tumor stage.

Previous studies reported an association between the number of excised LNs and survival in patients with clinically positive LNs [13, 14]. Our study adds meaningful information to these reports as it analyzes the highest number of patients ever enrolled for this purpose and included not only patients undergoing therapeutic LN dissection for clinically evident disease but also those undergoing completion LN dissection for a microscopic node metastasis detected with the SLNB technique.

Other studies have investigated the number of excised LNs relative to the number of positive LNs evaluating the so-called LN ratio [6–11]. Low values of this parameter (e.g. ≤0.1, which corresponds to 1, 2 or 3 positive LNs over ≥10, ≥20 or ≥30 excised LNs, respectively) were associated with better patient outcomes independently of the number positive LNs, leading to corroborate, though indirectly, the prognostic relevance of the number of excised LNs.

There are at least three possible explanations that might underlie the association between patient prognosis and the number of excised LNs: the prognostic value of the number of excised LNs, the therapeutic value of a thorough dissection and the immunological role of the LNs.

LN dissection has a pivotal staging role in melanoma as well as in virtually all solid tumors [15–17]. A thorough dissection allows for the removal and identification of all metastatic LNs, the number of positive LNs being one of the most important parameters of the AJCC N-stage [18]. The association we found between number of excised LNs and prognosis might be related to the better staging obtained in patients with a greater number of excised LNs at lymphadenectomy. For instance, a patient classified as AJCC N1 substage after a thorough lymphadenectomy is more likely to actually bearing only one metastatic LN when compared with a patient who underwent a more limited LN dissection, as demonstrated by the correlation between numbers of LNs removed and positive (Table 3). Furthermore, we observed a lower risk of death in the later study period when more LNs were excised (supplementary Table S1, available at *Annals of Oncology* online), supporting the principle of more accurate staging with more complete surgery.

In this regard, another finding of our study could be of particular interest, as we demonstrated that the AJCC N substages stratified survival of patients when at least 11 LNs were excised (Figure 1A and B). In order to provide minimum number of excised LNs for each nodal field, we identify that at least 14, 11, 10 and 12 LNs are required to stage patients after neck, axillary, inguinal and ilioinguinal dissection, respectively, according to the AJCC N substages (supplementary Figure S1, available at *Annals of Oncology* online).

Another attempt to define adequacy of lymphadenectomy based on the number of excised LNs was reported by Spillane et al., who identified minimum numbers of LNs to be excised according to the dissected anatomical boundaries within each nodal field, without accounting for patient survival [10, 19]. Ninety percent of patients had 10, 6, 20, 8 and 14 excised LNs after axillary dissection, neck dissection involving ≤3 or ≥4 anatomical levels, inguinal and ilioinguinal lymphadenectomy, respectively. Differently, our study analyzed melanoma-specific survival and identified a LN count that allows patient risk stratification according to the AJCC system. Despite the differences in the methodological approaches used in our study and in those from Spillane et al., their cutoff values for axillary, inguinal and ilioinguinal dissection are similar to those we identified. The relatively small number of patients who had a neck dissection in our study did not allow to group them according to the dissected neck anatomic levels, preventing a comparison with the results of Spillane et al. for this LN field. These results have implication for monitoring quality assurance of lymphadenectomy, given the general agreement about the use of the number of excised LNs as a measure to assess quality of surgery [12, 19, 20].

Showing that patients who had a higher number of excised LNs had also a better prognosis, this study lends support also to the alternative hypothesis that a thorough dissection might have a therapeutic effect. However, the design of this study cannot directly answer to the question of whether or not lymphadenectomy prolongs survival in patients with LN metastasis from melanoma, an issue that can be formally addressed only by a randomized trial. The randomized studies so far conducted in patients with clinically negative LNs at primary melanoma diagnosis have not demonstrated an impact on overall survival for immediate lymphadenectomy when compared with therapeutic lymphadenectomy carried out in patients with clinically evident disease [2, 3]. Evidence from the subgroup of patients with LN metastasis revealed better overall survival rates for those who underwent a completion dissection for a positive SLNB, particularly with intermediate thickness primary tumor [3, 4]. Intriguingly, results of subgroup analysis in our study lead to similar conclusions. In fact, the number of excised LNs was a prognostic factor in patients with intermediate thickness melanoma (but not in those bearing a thin or thick primary tumor) and in patients with LN micrometastasis but not in patients with macrometastasis. The observation that the prognostic value of the number of excised LNs seems limited to LN micrometastasis underlines the importance of considering timing of lymphadenectomy (early versus delayed) and LN tumor burden (micro versus macrometastasis) for accurate patient staging [21].

Finally, naturally occurring variability in number of LNs across individuals may theoretically have influenced the results of this study. Should this be the case, the findings of this study would lead to hypothesize that patients with a higher number of LNs in the regional field might have a better prognosis, putatively because of a more effective immune response.

This study might be limited by the lack of data regarding possible confounding factors, such as the body mass index, which theoretically may affect the number of LNs in a given nodal field and adjuvant therapies, such as interferon alpha [22] and radiotherapy [23], which influence patient outcomes.

In conclusion, this study demonstrated that the number of excised LNs at lymphadenectomy is significantly and independently associated with melanoma-specific survival and that a minimum number of LNs is required for the correct staging of patients. Further research is required to validate the prognostic effectiveness of minimum number of LNs to be excised at lymphadenectomy for melanoma.

References

1. Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol 2010;28:2452-2459.
2. Lens MB, Dawes M, Goodacre T, et al. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. Arch Surg 2002;137:458-461.
3. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307-1317.
4. Pasquali S, Mocellin S, Campana LG, et al. Early (sentinel lymph node biopsy-guided) versus delayed lymphadenectomy in melanoma patients with lymph node metastases: personal experience and literature meta-analysis. Cancer 2010;116:1201-1209.
5. Morton DL. Overview and update of the phase III Multicenter Selective Lymphadenectomy Trials MSLT-I and MSLT-II) in melanoma. Clin Exp Metastasis 2012;29:699-706.
6. Mocellin S, Pasquali S, Rossi CR, et al. Validation of the prognostic value of lymph node ratio in patients with cutaneous melanoma: a population-based study of 8,177 cases. Surgery 2011;150:83-90.
7. Rossi CR, Mocellin S, Pasquali S, et al. N-ratio: a novel independent prognostic factor for patients with stage-III cutaneous melanoma. Ann Surg Oncol 2008;15:310-315.
8. Spillane AJ, Cheung BL, Winstanley J, et al. Lymph node ratio provides prognostic information in addition to American joint committee on cancer N stage in patients with melanoma, even if quality of surgery is standardized. Ann Surg 2011;253:109-115.
9. Xing Y, Badgwell BD, Ross MI, et al. Lymph node ratio predicts disease-specific survival in melanoma patients. Cancer 2009;115:2505-2513.
10. Spillane AJ, Haydu L, McMillan W, et al. Quality assurance parameters and predictors of outcome for ilioinguinal and inguinal dissection in a contemporary melanoma patient population. Ann Surg Oncol 2011;18:2521-2528.
11. van der Ploeg AP, van Akkooi AC, Schmitz PI, et al. Therapeutic surgical management of palpable melanoma groin metastases: superficial or combined superficial and deep groin lymph node dissection. Ann Surg Oncol 2011;18:3300-3308.
12. Grotz TE, Huebner M, Pockaj BA, et al. Limitations of lymph node ratio, evidence-based benchmarks, and the importance of a thorough lymph node dissection in melanoma. Ann Surg Oncol 2013. September 18 [epub ahead of print], doi: 10.1245/s10434-013-3186-0.
13. Chan AD, Essner R, Wanek LA, et al. Judging the therapeutic value of lymph node dissections for melanoma. J Am Coll Surg 2000;191:16-22. discussion 22–13.
14. Galliot-Repkat C, Cailliod R, Trost O, et al. The prognostic impact of the extent of lymph node dissection in patients with stage III melanoma. Eur J Surg Oncol 2006;32:790-794.

15. Wong SL. Lymph node evaluation in colon cancer: assessing the link between quality indicators and quality. JAMA 2011;306:1139-1141.
16. Cascinelli N, Bombardieri E, Bufalino R, et al. Sentinel and nonsentinel node status in stage IB and II melanoma patients: two-step prognostic indicators of survival. J Clin Oncol 2006;24:4464-4471.
17. Gervasoni JE Jr., Sbayi S, Cady B. Role of lymphadenectomy in surgical treatment of solid tumors: an update on the clinical data. Ann Surg Oncol 2007;14:2443-2462.
18. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199-6206.
19. Spillane AJ, Cheung BL, Stretch JR, et al. Proposed quality standards for regional lymph node dissections in patients with melanoma. Ann Surg 2009;249:473-480.
20. Pasquali S, Spillane AJ, de Wilt JH, et al. Surgeons' opinions on lymphadenectomy in melanoma patients with positive sentinel nodes: a worldwide web-based survey. Ann Surg Oncol 2012;258:152-157.
21. Spillane AJ, Pasquali S, Haydu LE, et al. Patterns of recurrence and survival after lymphadenectomy in melanoma patients: clarifying the effects of timing of surgery and lymph node tumor burden. Ann Surg Oncol 2013. September 20 [epub ahead of print], doi: 10.1245/s10434-013-3253-6.
22. Mocellin S, Lens MB, Pasquali S, et al. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev 2013;6:CD008955.
23. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol 2012;13:589-597.