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ORIGINAL ARTICLE – MELANOMAS

Melanoma Patient-Reported Quality of Life Outcomes Following Sentinel Lymph Node Biopsy, Completion Lymphadenectomy, and Adjuvant Interferon: Results from the Sunbelt Melanoma Trial

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ABSTRACT

Background. Quality of life (QOL) and physical condition (PC) outcomes after sentinel lymph node biopsy (SLNB), completion lymph node dissection (CLND), and adjuvant therapy with interferon alfa-2b (IFN) were evaluated in this study.

Methods. Self-reported QOL and PC scores were evaluated in patients enrolled in a prospective, multicenter, randomized, clinical trial evaluating adjuvant IFN. After SLN biopsy, patients with a positive SLN underwent CLND then were randomized to adjuvant IFN or observation. QOL and PC scores were compared between patients who underwent SLNB alone, CLND without IFN, and CLND with IFN. Time to return to baseline QOL and PC scores reported at the time of SLNB was recorded and compared.

Results. There were statistically significant differences in time to return to baseline QOL ($p = 0.0018$) and PC ($p = 0.0018$) scores across the three treatment groups. The time to return to baseline QOL and PC scores was similar for SLND and CLND alone. Differences in time to return to baseline QOL and PC were sustained when stratified by recurrence status but did not differ significantly for different lymph node regions. There was a delay in return to baseline QOL and PC condition scores that was sustained beyond the cessation of IFN therapy.

Conclusions. CLND is well-tolerated with a similar effect on self-reported QOL outcomes in both the short- and long-term compared with SLNB alone. IFN therapy is associated with worse QOL outcomes compared with SLNB and CLND, an effect that may be sustained following cessation of adjuvant IFN.

Current treatment for cutaneous melanoma without evidence of metastatic disease is wide local excision with sentinel lymph node (SLN) biopsy. This approach improves survival in patients with SLN positive disease over observation alone.[1] A positive SLN is usually treated with a subsequent completion lymph node dissection (CLND) of the involved nodal basin in an effort to further identify non-SLN metastases and to clear additional micrometastatic nodal disease.[2–5] In clinical practice, CLND is not performed following a positive SLN biopsy as frequently as expected.[6] Some authors have proposed selective observation of SLN positive patients without CLND, citing similar survival results in select patients and increased morbidity of a CLND.[7,8] More information regarding morbidity and quality of life (QOL) outcomes after CLND is needed to completely explain the risks, benefits, and expected outcomes to patients before recommending a CLND.

Micrometastatic stage III melanoma carries a wide range of prognosis.[9] Interferon α-2b (IFN) has been tried in various forms as an adjuvant therapy in high-risk stage III melanoma in an effort to improve disease-free and overall

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survival. Results from these studies have in general shown improvement in disease-free survival but variable impact on overall survival.[10–15] IFN therapy has profound side effects and is associated with decreased QOL measures.[15–18] Whereas there may be select high-risk groups that benefit from IFN, the expected QOL outcomes and the duration of side effects from IFN remain to be well defined. This study was performed in an effort to analyze patient-reported, prospectively collected QOL outcomes from a multicenter, randomized, prospective clinical trial in an effort to answer two questions: (1) how do patient-reported QOL outcomes after CLND compare to SLN biopsy alone, and (2) what are the patient-reported QOL outcomes following a short and long course of adjuvant IFN therapy.

MATERIALS AND METHODS

Results from the Sunbelt Melanoma Trial were reviewed for this study. The Sunbelt Melanoma Trial was a multicenter, randomized, prospective clinical trial. Participation in the trial was approved by each institution's review committee. The schema of the study has been described previously.[19] Patients with a histologically or immunohistochemically positive SLN underwent a CLND and were enrolled in Protocol A. Patients with only a single positive SLN were randomized to observation or adjuvant IFN therapy as defined in Protocol A. All patients with more than one positive SLN, extracapsular extension, or a positive non-SLN were treated in a nonrandomized manner with adjuvant IFN. Patients who were histologically or immunohistochemically negative on SLN biopsy were enrolled in Protocol B, in which the SLNs were further analyzed with RT-PCR. Patients positive by PCR analysis were randomized to observation, CLND, or CLND plus adjuvant IFN therapy. Patients whose SLNs were negative by PCR were observed. The interferon course for patients with positive SLNs in Protocol A was high-dose intravenous infusion at 20 MU/m^2/dose 5 days per week for 4 weeks, followed by three times per week subcutaneous treatments of 10 MU/m^2/dose for 48 weeks. For patients in Protocol B who were positive only be PCR, the IFN course was initially the same as Protocol A; however, in 1999 the protocol was amended and only a short course of 4 weeks of intravenous IFN only at the dose described above was given. The majority of patients treated with IFN in Protocol B (75 %) received the short course only.

At the time of enrollment, all patients completed a baseline QOL questionnaire in which they were asked:

(1) Prior to your diagnosis of your melanoma, how would you rate your overall physical condition (PC)?
(2) Prior to your diagnosis of your melanoma, how would you rate your overall QOL?

Responses were given on a 1–10 scale with 1 being "Very Poor" and 10 being "Excellent." These are the baseline PC and QOL scores. Additionally, at each follow-up visit, patients were asked:

(1) Since your last visit, how would you rate your overall PC?
(2) Since your last visit, how would you rate your overall QOL?

These are the follow-up PC and QOL scores. Also, patients at each follow-up visit were asked a series of yes/no questions regarding whether they had experienced or felt a specific complaint since their last visit. The presence of each of these specific complaints were associated with lower PC and QOL scores (Supplementary Fig. 1).

Clinicopathologic factors for each treatment group were compiled and analyzed. Comparisons were made with ANOVA or Chi square tests, as appropriate. The time to return to baseline PC or QOL was defined as the first follow-up point at which the patient reported an absolute PC or QOL score greater than or equal to their baseline score. Follow-up times were rounded to the nearest 3-month interval. Groups of interest were compared with Cox proportional hazard models. Multivariate models were created using factors that on univariate analysis were statistically significant. Time to return to baseline also was charted using Kaplan–Meier curves and compared with the log-rank test. Repeated measures ANOVA was used to compare mean QOL and PCs scores over time by treatment group. Mean QOL and PCs scores were compared by ANOVA in the presence or absence of specific complaints. Only patients who had a baseline survey and at least one follow-up survey, and who were confirmed to have received their assigned treatment, were included in this study. All tests were two-sided and the level of statistical significance was set at <0.05.

RESULTS

This study identified 490 patients with QOL survey results for analysis. For the SLN only group, the rate of positive SLN biopsy was 24.3 %. The total number of lymph nodes removed in the CLND alone vs CLND + IFN groups were similar (median 16 and 15, $p = 0.53$), as was the rate of positive non-SLNs for CLND (11.9 %) and CLND + IFN (16.4 %, $p = 0.35$). The complication rate from SLN biopsy alone was 5.9 %. The complication rate for CLND alone was 22.9 %, which was not statistically different from the complication rate for CLND + IFN (25.5 %, $p = 0.66$).

At the time of enrollment, the baseline reported QOL and PCs scores were similar between the two groups.

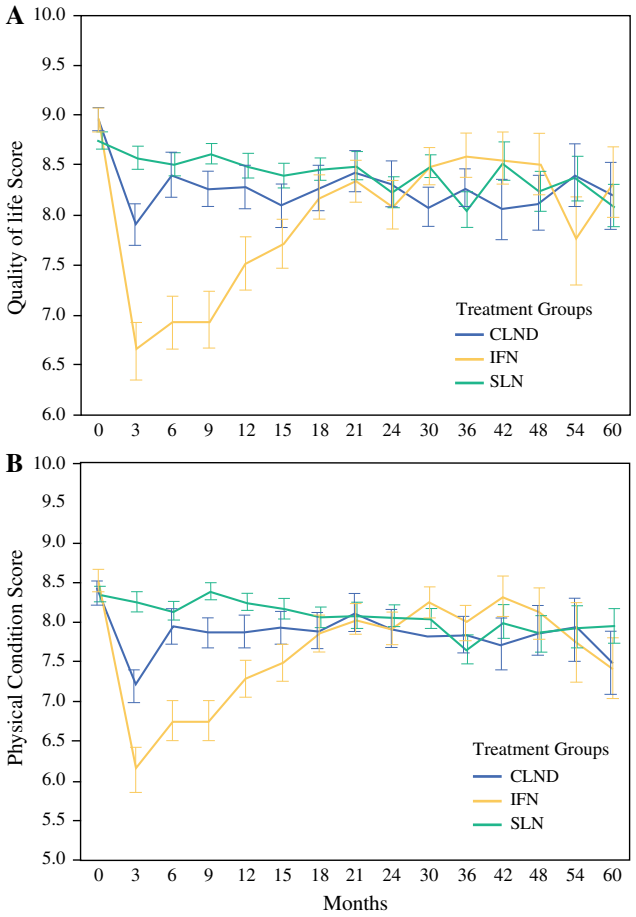

FIG. 1 Quality of life (**a**) and physical condition (**b**) scores over time for SLN alone, CLND alone, and CLND + adjuvant interferon therapy

Median baseline QOL scores for the SLN alone, CLND, and CLND + IFN groups were 9, 9, and 9 ($p = 0.27$) and median baseline PC scores were 10, 10, and 9 ($p = 0.58$). Figure 1 demonstrates the trend in the absolute values of the QOL scores and PC scores over time. Scores for the CLND alone group trended back to the SLN group after 3 months, whereas the scores for the CLND + IFN group remained less than the other two groups. Over time, there was a significant difference in both QOL scores and PC scores for the CLND + IFN group compared with the SLN alone group ($p = 0.0007$ and 0.0033, respectively), but not for the CLND group compared with the SLN alone group ($p = 0.18$ and $p = 0.46$, respectively). There were no significant differences in treatment groups in either score after 21 months. When analyzed by specific complaints, both QOL and PC scores were lower in the presence of every specific complaint analyzed (Supplementary Fig. 1).

Time to return to baseline QOL and PC scores were then analyzed and compared across the treatment groups. Treatment with CLND + IFN (compared with SLN or CLND alone) was the only independent risk factor for a delay in return to baseline score for both QOL and PC scores (Table 1). Kaplan–Meier curves demonstrate that while the proportion of patients who returned to baseline PC or QOL scores over time was similar between the SLN alone and CLND alone groups, there was a delay in return to baseline scores in the CLND + IFN group (Fig. 2). When stratified by recurrence versus nonrecurrence, the same pattern of delay in return to baseline QOL and PC scores was apparent (Fig. 3).

The CLND + IFN groups were then separated into the short-course group and the long-course group. There were statistically significant differences in the time to return to baseline QOL and PC scores across these four groups. The time to return to baseline showed a similar pattern for the short- and long-course IFN groups; only after approximately 24 months did the proportion of patients reporting a return to baseline treated with short or long course of IFN approach that of those patients treated with either SLN or CLND alone (Fig. 4). When compared by lymph node dissection site (axillary, inguinal, or neck), there were no differences in the time to return baseline QOL ($p = 0.79$) or baseline PC scores ($p = 0.88$) (Supplementary Fig. 2).

DISCUSSION

The findings in this study demonstrate that CLND is well tolerated by patients, with similar self-reported QOL and PCs outcome scores in both the short and long term. This suggests that concerns about lifestyle limiting comorbidities should not be a major deterrent to the recommendation of CLND following SLN biopsy, when warranted by the clinical situation. This study also demonstrates that the addition of adjuvant IFN following CLND has a measurable and prolonged effect on self-reported QOL and PC that extends beyond the actual treatment course of IFN.

Previous studies of patients who forgo CLND after a positive SLN biopsy in favor of observation suggest that the oncologic outcomes are not demonstrably worse for this cohort of patients compared with those who undergo CLND.[7,8] Concerns about the comorbidities associated with CLND, particularly in elderly patients or those with medical comorbidities such as obesity, are commonly cited reasons to recommend against CLND after a positive SLN biopsy in our own practice. The findings in this study demonstrate that a CLND is well tolerated and has comparable self-reported QOL and PC outcomes to that of SLN biopsy alone. These favorable outcomes are sustained over time.

Perioperative morbidity, as measured by postoperative surgical complications, is certainly less in SLN biopsy alone compared with SLN biopsy followed by CLND. The largest series report SLN complication rates on the order of

TABLE 1 Risk factors for a delay in return to baseline quality of life and physical condition scores

Factor	Multivariate hazard ratio (95 % confidence interval)	Multivariate *p* value
Quality of life scores		
Breslow thickness	1.02 (0.96, 1.02)	0.53
Lymphovascular invasion	1.50 (0.97, 2.45)	0.07
Clark level ≥ IV	1.22 (0.94, 1.57)	0.14
Positive SLN	1.01 (0.73, 1.36)	0.97
Treatment		
SLN	–	
CLND	–	
IFN	1.52 (1.11, 2.10)	0.0079
Physical condition scores		
Age	0.99 (0.98, 1.00)	0.18
Clark level ≥ IV	1.21 (0.94, 1.55)	0.14
Positive non-SLN	1.57 (0.80, 3.56)	0.20
Treatment		
SLN	–	
CLND	–	
IFN	1.38 (1.04, 1.85)	0.0242

SLN sentinel lymph node, *CLND* completion lymph node dissection, *IFN* adjuvant interferon therapy

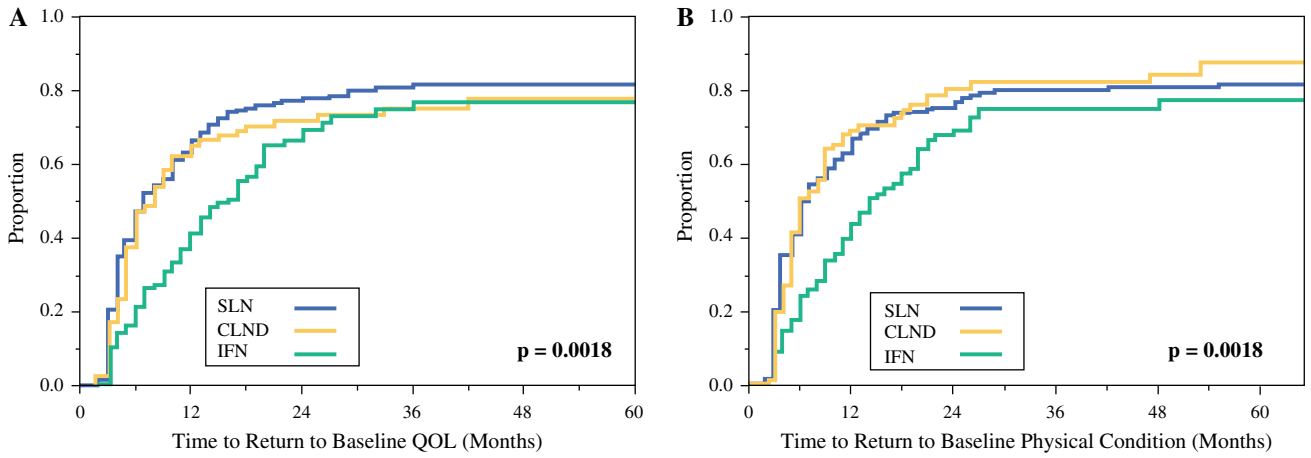

FIG. 2 Time to return to baseline quality of life scores (**a**) and physical condition scores (**b**) according to treatment arm

5–10 %, with an approximate three- to fourfold increase in the complication rates (23–37 %) for SLN biopsy followed by CLND.[20,21] While the objectively measured complication rates, meticulously recorded in prospective clinical trials, show obvious morbidity differences between SLN biopsy and CLND, these differences may not be relevant to the subjective self-reported QOL outcomes of the patients. Few studies have reported patient-centered QOL outcomes after CLND and SLN biopsy. In a series comparing 89 patients with SLN alone to 27 patients undergoing CLND, de Vries et al. found that while the complication rates and lymphedema rates were higher in the CLND, for most categories of QOL measurements captured by their instruments, there were not statistically significant differences in QOL outcomes among the SLN and CLND groups when stratified by axillary or inguinal site.[22] Interestingly, they reported trends towards decreased QOL outcomes in patients with CLND in the axilla compared with the SLN alone patients.[22] Our findings demonstrate the CLND is equally well tolerated from a QOL perspective regardless of the lymph node basin. In this study, we found that CLND is well tolerated despite higher perioperative complication rates; over time, QOL outcomes mirror those of SLN biopsy.

Adjuvant IFN has a profound and sustained negative effect on self-reported QOL and PC outcomes in stage III

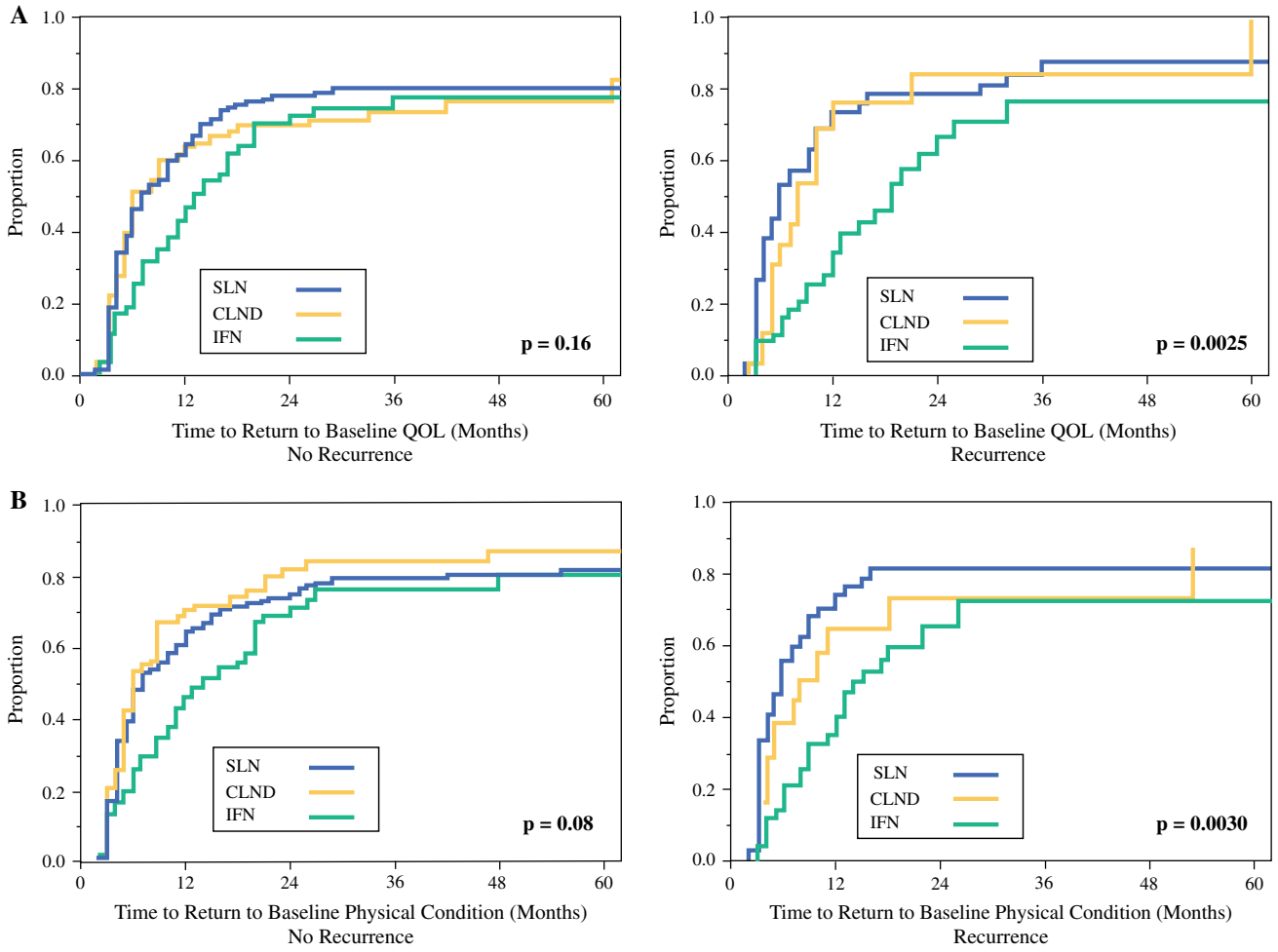

FIG. 3 Time to return to baseline quality of life (**a**) and physical condition (**b**) scores, stratified by the presence of absence of recurrent disease

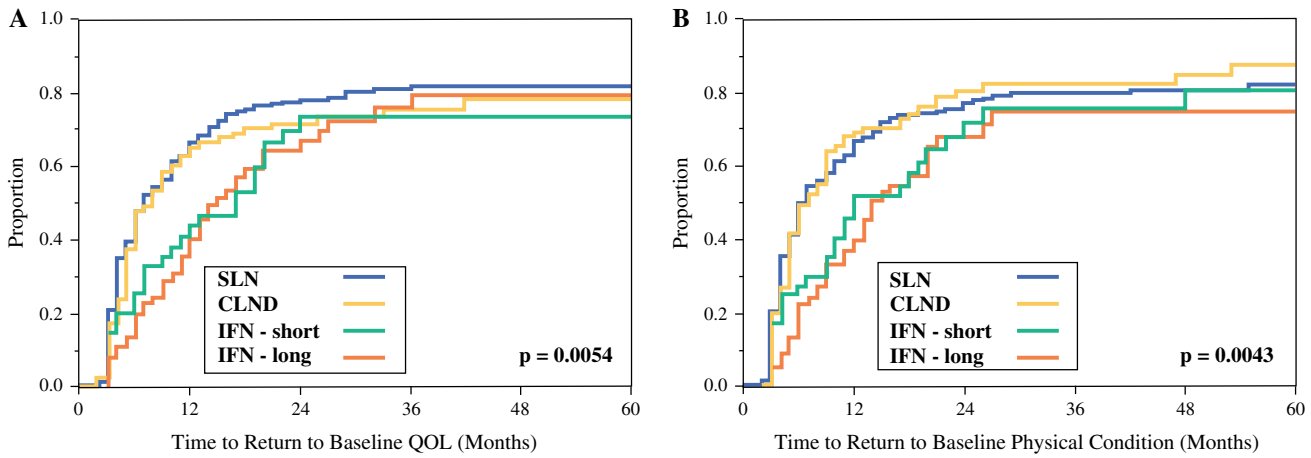

FIG. 4 Time to return to baseline quality of life (**a**) and physical condition (**b**) scores, considering both short and long course adjuvant IFN therapy

melanoma. Only after approximately 2 years does the proportion of patients reporting a return to baseline QOL and PC approach that of SLN or CLND alone. Several studies have used the EORTC QLQ-C30 instrument to confirm reduction in QOL measurement in both IFN and pegylated IFN compared to observation alone in stage III

melanoma.[16,17] Findings from the DeCOG study confirm the prolonged deterioration in QOL scores associated with IFN therapy and suggest that cognitive dysfunction may be an important side effect.[23] Results from the Nordic Adjuvant IFN trial also showed a profound negative effect of IFN therapy compared with observation and reported a delay in return to baseline QOL after cessation of IFN.[18]

The similar pattern of time to return to baseline QOL and PC scores for the short-or long-course IFN therapies suggests that most of the toxicity is related to the 1-month intensive intravenous IFN therapy. Results from the randomized phase III trial run by the Hellenic Cooperative Oncology Group, in which the same two IFN therapies used in this study were compared, support this conclusion, because they report that toxicities were similar between the two IFN courses; no self-reported QOL outcome were reported with this trial.[24] The findings in this study and others allow clinicians to more fully inform prospective patients about the long-term QOL outcomes that can be expected with adjuvant IFN therapy and the recovery period that can be anticipated. The profound and prolonged effects of adjuvant IFN on QOL outcomes, the controversial oncologic benefit of adjuvant IFN, and the individual patient's risk of recurrence all must be considered in making adjuvant therapy decisions.

The strengths of this study include the prospectively collected nature of the QOL data and the randomization between CLND and CLND + IFN groups to better balance relevant clinicopathologic factors. We report a simple two question instrument to assess repeatedly patient's perceived QOL and PC outcomes. A strict definition of return to baseline score was used as the primary endpoint in this study. Use of this endpoint allows simple, straightforward statistical time-to-event analyses using Cox proportional hazard modeling and survival analysis to account for censored and missing data. The longitudinal nature of the study allows one to assess the changes in QOL and PC scores over time and to define the recovery period, rather than simply assessing outcomes at an arbitrary, fixed time point retrospectively. Limitations of the study also need to be considered. The assessment tool used was not as extensive as the EORTC QLQ C-30 discussed above or the previously reported, melanoma specific, FACT-Melanoma questionnaire.[25] The simplicity of our instrument does not allow one to identify specific areas of health-related QOL outcomes that are differentially affected by the interventions of interest, rather it allows a global assessment of how the patient perceives their own health and well-being. However, it is important to note that the QOL and PC scores were significantly lower in the presence of each specified complaint that was measured, thus the overall QOL and PCs scores are capturing the presence or absences of specific complaints (Supplementary Fig. 1). The relatively strict definition of return to baseline QOL and PC scores may somewhat underestimate how well patients perceive that they are doing.

In conclusion, this study found that patient-reported outcomes were similar between those who underwent SLN biopsy alone versus SLN biopsy plus CLND. Adjuvant IFN therapy after CLND had a profound and prolonged effect on patient-reported outcomes that extend beyond the actual treatment course.

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