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Original Research

Surgical outcomes of lymph node dissections for stage III melanoma after neoadjuvant systemic therapy are not inferior to upfront surgery

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Abstract ***Background:*** Neoadjuvant systemic therapy has shown promising results in the treatment of high-risk stage III melanoma; however, the effects on surgery are currently unknown. This study aims to compare the surgical outcomes, in terms of postoperative complications, postoperative morbidity, duration of surgery and textbook outcomes, of patients with high-risk stage III melanoma who received neoadjuvant systemic therapy followed by lymph node dissection with patients who received an upfront lymph node dissection.
Methods: In this retrospective cohort study, patients with high-risk stage III melanoma treated with neoadjuvant anti-PD1 and anti-CTLA4 in the OpACIN (NCT02437279) and

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OpACIN-neo (NCT02977052) trial between October 2014 and August 2018 were included and compared to patients who received upfront surgery in the same time period.
Results: A total of 120 patients were included in this study, of whom 44 received neoadjuvant systemic therapy and 76 underwent upfront surgery. There was no significant difference in the overall rate of postoperative complications between the neoadjuvant group and the upfront surgery group (31.8% versus 36.8%, p = 0.578) and neither in rate of postoperative morbidity (seroma 56.8% versus 57.9%, p = 0.908) (lymphedema 22.7% versus 13.2%, p = 0.175). There was a non-significant difference towards a slightly longer duration of surgery after neoadjuvant immunotherapy (105 versus 90 min, p = 0.077). There were no differences in textbook outcomes (50% versus 49%, p = 0.889).
Conclusion: This study shows that the surgical outcomes for patients who underwent a lymph node dissection after neoadjuvant systemic immunotherapy or underwent upfront lymph node dissection for high-risk stage III melanoma are comparable.

1. Introduction

The use of systemic therapy with immune checkpoint inhibitors (ICI) and targeted therapies (TT) for the treatment of high-risk stage III melanoma has evolved in recent years and interest is shifting from use in the adjuvant setting to use in the neoadjuvant setting. Some proposed benefits of systemic treatment while the tumour is still *in situ* are to induce a broader T-cells response and thereby achieve higher recurrence-free survival (RFS) and overall survival (OS) as well as to be able to tailor the subsequent therapy to the response to neoadjuvant therapy. Several trials have already been published showing promising first results in terms of high overall response rates (ORR), major pathologic response (MPR) rates (pathologic complete response (pCR) and near-pCR) and recurrence-free survival [1–4]. Importantly, recently the randomised SWOG 1801 trial presented a significantly higher 2-year event-free survival for patients treated with three cycles of neoadjuvant pembrolizumab compared to the same dosing of adjuvant pembrolizumab [5]. More studies are on their way to address the question whether neoadjuvant systemic therapy does indeed improve survival compared to the current standard of care with an upfront lymph node dissection and adjuvant therapy, amongst others the NADINA trial (NCT04949113).

Preoperative systemic treatment with ICI or TT could in theory influence the technical difficulty and postoperative complications of lymph node dissections due to lymphocytic tissue infiltration and fibrosis [6]. In other cancers, the effects of neoadjuvant therapy on surgery and postoperative outcomes have been studied and described. For example, in breast cancer, neoadjuvant chemotherapy did not have an adverse effect on complications after breast surgery [7]. In melanoma, it is currently unknown what the effects of preoperative systemic treatment are. To our knowledge, only two studies reported on the resectability as assessed by the surgeon. One recent study described the change in technical difficulty of surgery as assessed by the surgeon before and after neoadjuvant TT. This study found that surgery after neoadjuvant treatment was more often assessed to be easier than estimated at baseline [8]. In addition, another trial investigating the effect of neoadjuvant TT also described an improvement in resectability as assessed by the surgeon [4].

More detailed data on postoperative complications following neoadjuvant immunotherapy adds to the knowledge required for the multidisciplinary treatment of patients with high-risk stage III melanoma [9]. In our centre, the Netherlands Cancer Institute, several neoadjuvant trials for macroscopic stage III melanoma have been performed and others are currently accruing. In addition, patients who receive upfront lymph node dissection are prospectively registered in a biobank linked to clinical data. These two cohorts of patients provide useful data on the effect of neoadjuvant systemic therapy on surgery. This study aims to compare the surgical outcomes of patients with high-risk stage III melanoma who received neoadjuvant systemic therapy followed by a lymph node dissection with patients who received upfront surgery. Primary endpoints are the rate and type of postoperative complications and morbidity. Secondary outcomes are the textbook outcome, as a novel composite measure of surgical outcomes, and duration of surgery.

2. Methods

This study is a retrospective cohort study of patients who underwent either upfront lymph node dissection, or lymph node dissection after neoadjuvant systemic therapy for stage III melanoma at the Netherlands Cancer Institute between 2015 and 2021. Patients were selected from our prospective biobank for stage III melanoma and from two completed neoadjuvant trials performed at our institution (OpACIN and OpACIN-neo) [10,11]. Patients who were not eligible for, or opted out of treatment in either one of the trials received the standard care of upfront surgery and were included in

the prospective biobank. The OpACIN and OpACIN-neo trial investigated the effectivity of neoadjuvant anti-PD1 inhibitor (nivolumab) in combination with an anti-CTLA4 inhibitor (ipilimumab) in different dosing and interval schemes. All patients underwent a complete lymph node dissection in accordance with international surgical guidelines. Ilioinguinal lymph node dissections were performed for patients with preoperative evidence of iliac lymph node metastases. If no iliac metastases were present, an inguinal lymph node dissection was performed. According to our local protocol, for the axillary and iliac lymph node dissections the surgical drain is removed after 1 day and for inguinal dissections the drain is removed after 3 d, irrespective of the production volume. After a neck dissection, the drain is removed if the production is < 15 ml per 8 h. Patients who underwent selective lymph node picking or another surgical procedure in the same operation session were excluded. N-stage was reported based on pathological examination of the surgical specimen. The duration of surgery was measured from the moment of incision to the completion of the surgical procedure. Data were extracted from their medical records and operative reports. The trials and biobank were approved by the Institutional Research Board (IRB)(NCT02437279, NCT02977052, BAVL50), and informed consent was obtained from all included patients.

Complications were evaluated according to the Clavien-Dindo classification (CD) at 1 and 3 months postoperatively. Only grade ≥II surgical complications were analysed. Wound infection was scored grade II if treated with oral or intravenous antibiotics and grade III if treated by surgical or radiological intervention. Wound dehiscence and haematoma managed at the bedside were scored grade I; if surgical intervention or vacuum-assisted closure therapy was necessary, it was scored as grade III. Postoperative morbidity was defined as seroma that required aspiration and lymphedema for which manual lymphatic drainage was prescribed. Preoperative immune-related Adverse Events (irAE) were classified according to the common terminology criteria for adverse events version 4(CTCAE v4).

Textbook outcome is a composite measure of positive short-term surgical outcomes and has been widely used for analysis and comparison of (non-oncological) surgical outcomes in other surgical fields, such as colorectal and aorta surgery [12–14]. Here we defined a textbook outcome as no reoperation within 30 d, R0 resection, no prolonged hospital stay (< 75th percentile), no re-admission (within 90 d) and no grade II-V complications within 90 d. R0 resection was defined as lymph node dissection with clear surgical margins.

2.1. Statistics

Descriptive statistics of patient characteristics were summarised by mean and standard deviation and compared by an unpaired t-test for continuous normally distributed variables. If not normally distributed median and interquartile ranges were shown and a comparison was made using a Mann-Whitney U test. Discrete variables were summarised in percentages and compared using Fisher's exact- or chi-square test. Odds ratios were calculated using the standard definition. Statistical significance was assumed at a p-value of < 0.05. IBM SPSS Statistics version 27 for windows was used for statistical analysis.

3. Results

3.1. Patient characteristics

A total of 120 patients were included in this study, of whom 44 received neoadjuvant systemic therapy and 76 underwent upfront surgery. Patients in the neoadjuvant group were younger on average (53 versus 60 years, $p = 0.011$) and in both groups a slight majority was male (55% and 54%). A majority of the included patients had melanoma of the extremities (41% and 50%) and most lymph node dissections were performed on the axillary nodal basin (59% and 50%). Patients in the neoadjuvant group had a significantly lower nodal tumour load ($p = 0.001$) (Table 1). Sentinel lymph node biopsy (SLNB) in the same nodal basin prior to lymph node dissection (LND) was performed in 67 patients (86%) and less often in the neoadjuvant group than the upfront surgery group (43% versus 63%, $p = 0.034$). In this cohort, all patients proceeded to surgery as planned without delay. In the original trial, there was a delay in surgery in six patients, and three patients did not proceed to surgery as planned due to distant visceral progression of disease and adverse events. These patients were excluded from this cohort previously due to other exclusion criteria.

3.2. Complications of surgery

There was no significant difference in the overall rate of complications in the neoadjuvant-treated group compared to the upfront surgery group (31.8% versus 36.8%, $p = 0.578$). In a subanalysis of rate of complications within 30 d and at 1–3 months, there was no statistically significant difference within 30 d (29.5% versus 21.1%, $p = 0.235$). However, there was a significantly higher rate of complication at 1–3 months postoperatively in the upfront surgery group (9.1% versus 25%, $p = 0.033$) (Fig. 1A). Within 30 d, in the neoadjuvant group wound infections were seen in 25%, wound dehiscence and haematoma that required surgical treatment in 4.5% and chyle leakage in 2.3%, while in the upfront surgery group wound infections were seen in 19.7%, wound dehiscence in 5.4%, postoperative haematoma that required surgery in 2.6%, and wound necrosis in 1.3%. In the neoadjuvant group there were

Table 1
Patient characteristics of included patients, categorised by group.

Variable	NAST (n = 44)	Upfront surgery (n = 76)	*p*
Age (mean, SD)	52.8 ± 14.7	59.9 ± 14.5	**0.011**
Gender (n,%)			0.949
Male	24 (54.5%)	41 (53.9%)	
Female	20 (45.5%)	35 (46.1%)	
Location primary melanoma (n,%)			**0.007**
Extremities	18 (40.9%)	38 (50.0%)	
Trunk	11 (25.0%)	31 (40.8%)	
Head-neck	3 (6.8%)	1 (1.3%)	
Unknown primary	12 (27.3%)	6 (7.9%)	
Breslow depth (Median, IQR)	2.0 (0.9–3.2)	2.2 (1.3–3.0)	0.055
Ulceration (n,%)			0.484
Absent	18 (40.9%)	43 (56.6%)	
Present	10 (22.7%)	17 (22.4%)	
T stage			0.061
Unknown	12 (27.3%)	10 (13.2%)	
pT1	12 (27.3%)	9 (11.8%)	
pT2	8 (18.2%)	22 (28.9%)	
pT3	7 (15.9%)	22 (28.9%)	
pT4	5 (11.4%)	13 (17.1%)	
N stage			**0.001**
pN1	24 (54.5%)	25 (32.9%)	
pN2	17 (38.6%)	21 (27.6%)	
pN3	3 (6.8%)	30 (39.5%)	
Dissection type			**0.043**
Neck	5 (11.4%)	4 (5.3%)	
Axillary	26 (59.1%)	38 (50.0%)	
Iliac	0	1 (1.3%)	
Inguinal	2 (4.5%)	18 (23.7%)	
Iliac+inguinal	11 (25.0%)	15 (19.7%)	
Number of resected nodes			
Neck	46	40	0.806
Axillary	29	26	0.419
Iliac		14	
Inguinal	5	9	0.128
Iliac+inguinal	21	22	0.488
Pathological response			
(near-) complete response	23 (52.3%)		
Partial response	6 (13.6%)		
Non-response	15 (34.15%)		
SLNB prior to LND (n, %)	19 (43%)	48 (63%)	**0.034**

Significant p-values are shown in bold. N-stage is based on pathological examination of surgical specimen.

grade II events in 29% and grade III in 16% according to the Clavien-Dindo classification, while in the upfront surgery group grade II events occurred in 37.2% and grade III events in 2.3%. In both groups there were no grade IV and V events. At 1–3 months after resection, only infections occurred and were grade II in both groups. The rate of complications significantly differed between the anatomical type of lymph node dissection (p = 0.002). The overall rate of complications within 3 months was 21.9% for axillary, 51.9% for ilioinguinal (including one iliac lymph node dissection), 60% for inguinal and 22.2% for neck lymph node dissections (Fig. 1C). SLNB prior to LND had no significant effect on the overall incidence of complications (OR 1.5, 95% CI 0.7–3.1, p = 0.3).

3.3. Postoperative morbidity

There was no overall difference in rate of seroma that required aspiration between the neoadjuvant group and the upfront surgery group (56.8% versus 57.9%, p = 0.908). Within 30 d, there was no significant difference either (54.5% versus 46.1%, p = 0.370). However, there was a significantly higher rate of seroma aspiration in the adjuvant surgery group at 1–3 months postoperatively (15.9% versus 32.9%, p = 0.043). There were no significant differences in rate of lymphedema (overall rate 22.7% versus 13.2%, p = 0.175) (Fig. 1B). SLNB prior to lymph node dissection in the same nodal basin did not have a significant influence on the occurrence of seroma or lymphedema.

3.4. Surgery time and textbook outcome

The mean duration of surgery did not significantly differ between the neoadjuvant-treated and upfront surgery group, although there was a non-significant difference towards a shorter duration of surgery in the upfront surgery group (105 versus 90 min, p = 0.077). In a subgroup analysis, surgery time per region of lymph node dissection was compared for neck dissection (194.4 versus 178.5, p = 0.462), axillary dissection (78.7 versus 79.6 min, p = 0.854) and ilioinguinal dissection (131 versus 114.4 min, p = 0.072) (Fig. 1D). Duration of surgery was not significantly longer if a surgical registrar performed the surgery compared to a consultant (99.1 versus 91.2 min, p = 0.3). There was no significant difference in percentage of patients in whom a textbook outcome was achieved (50% versus 49%, p = 0.889) (Fig. 2). Furthermore, subanalysis of the separate parameters did not show any significant differences between the groups.

3.5. Immune-related adverse events

Immune-related adverse events (irAE) occurred in 26 patients (59%) prior to surgery. Of those patients, 19 (73%) were treated with oral corticosteroids and 17 (65%) were still on steroid treatment at the time of surgery. One patient experienced an Addisonian crisis prior to surgery and was treated with a stress dose of hydrocortisone at the time of surgery. There was no increased risk of postoperative surgical complications for patients who received corticosteroid treatment for irAE (OR 1.05, 95%CI 0.71–1.6, p = 1.0.).

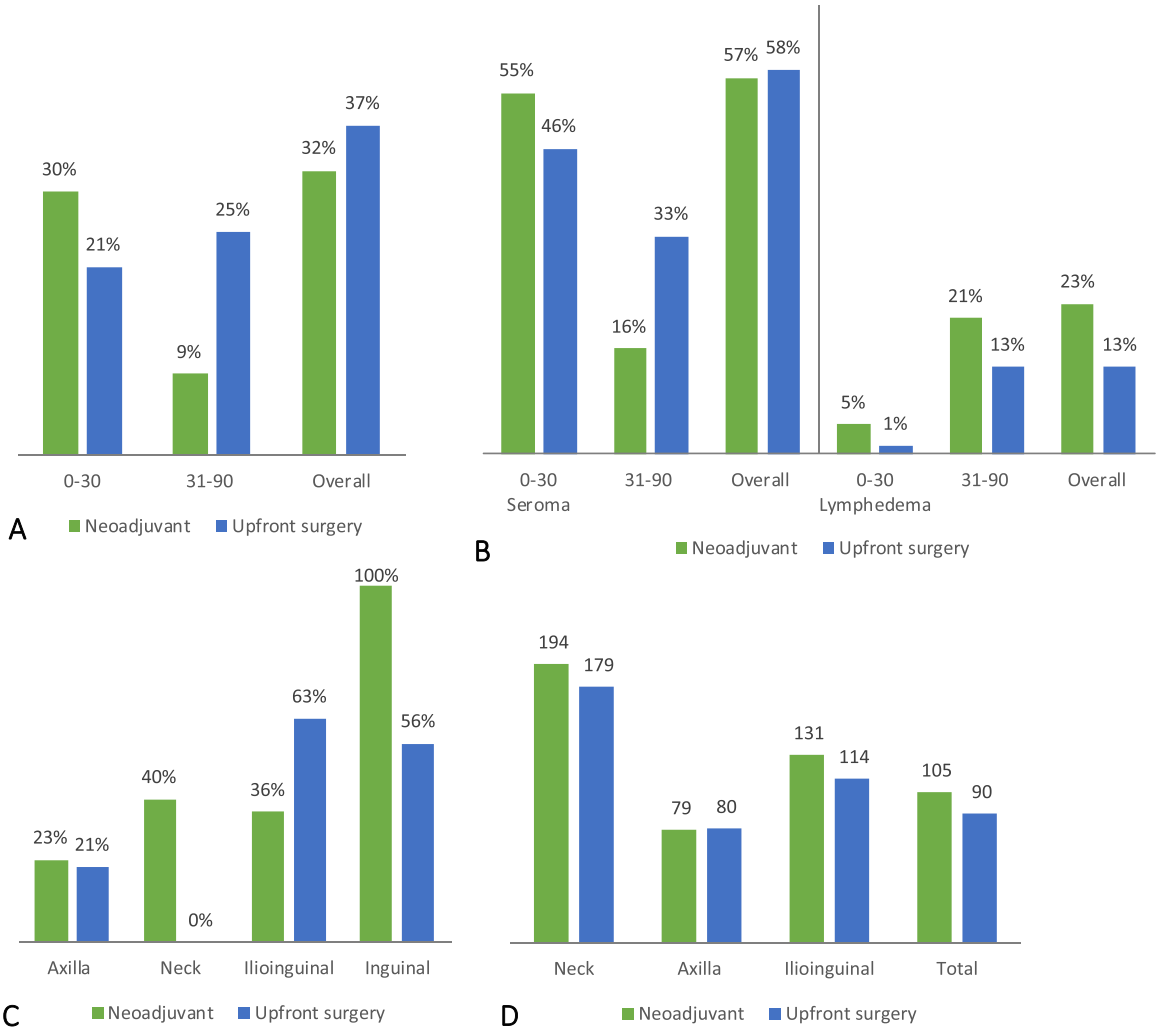

Fig. 1. Rate of complications (CD grade ≥ 2) for neoadjuvant-treated and upfront surgery patients. (A) Rate of complications within 30 days, after 1–3 months and overall. (B) Postoperative morbidity within 30 d, after 1–3 months and overall. (C) Total rate of complications per anatomical location of lymph node dissection. (D) Duration of surgery per anatomical location in minutes.

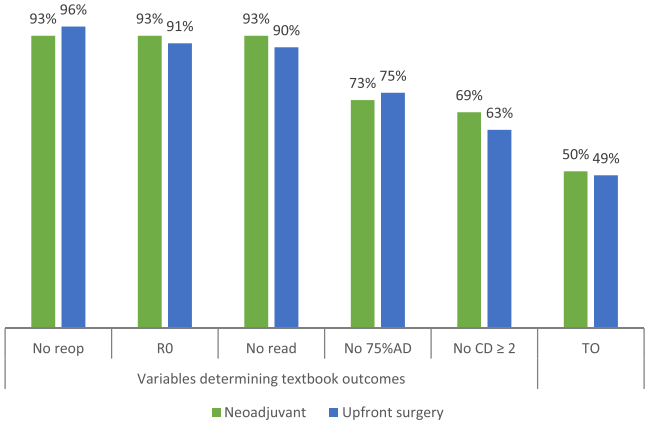

Fig. 2. Parameters of textbook outcome displayed per group. No reop: percentage of patients who did not undergo reoperation. R0: percentage of patients who had a R0 resection. No read: percentage of patients that were not readmitted. No 75%AD: percentage of patients who had a duration of admission within the 75 percentile. No CD ≥ 2: percentage of patients who did not experience a grade > 2 complications according to the Clavien-Dindo classification. TO: percentage of patients who met our definition of textbook outcome.

4. Discussion

This study assessed the surgical outcomes of patients who received a lymph node dissection after neoadjuvant systemic therapy or upfront lymph node dissection for stage III melanoma. In this selected patient group, the surgical outcomes were comparable in terms of postoperative complications, postoperative morbidity, duration of surgery and textbook outcomes.

The overall rate of complications was not significantly different between the groups. However, interestingly the rate of complications at 1–3 months was significantly higher in the upfront surgery group. In contrast, the rate of complications in the first month seems higher for the neoadjuvant treatment group, but is lacking statistical significance. The data suggests complications such as infection and wound dehiscence develop earlier in patients treated with neoadjuvant systemic immunotherapy. One obvious hypothesis to explain this would have been the potential use of steroids to treat immune-related adverse events caused by the neoadjuvant systemic therapy. However, the use of steroids was not associated with the occurrence of postoperative surgical complications. Whether this observation is an effect of systemic immunotherapy prior to surgery or the numbers in this study are simply too small remains unclear; future studies must show whether this is also observed in other neoadjuvant trials. Of note, the patient treated in the upfront surgery group were significantly older, had higher stage disease and were more often undergoing inguinal dissections, which might potentially influence these results. The rate of complication reported here is similar to the rate of complications reported for lymph node dissections in other studies. For inguinal dissections, other studies report a complication rate of 51.2−77.4%, including seroma aspirations [15–17]. The rate of complications for groin dissections is known to be higher than other dissections, as is also shown in this study. Only a select number of studies have studied the effect of neoadjuvant systemic therapy on perioperative outcomes. A study by Sun et al. described a complication rate of 24% for 63 patients who received ICI or TT prior to surgery [18]. Furthermore, a small study by Gyorki et al. described a complication rate of 22% for 24 patients who underwent surgery after treatment with ipilimumab [6]. However, both studies included various operations, various treatments prior to surgery and for various stages of melanoma, and did not include a reference group.

Seroma requiring needle aspiration after early removal of the drain and lymphedema are expected effects of a lymph node dissection, and therefore in this study described separately as postoperative morbidity. The same trend as for complications was observed here, with significantly higher rates of seroma aspirations at 1–3 months postoperatively in the upfront surgery group. Again, the rate of aspirations within 30 d was higher for the neoadjuvant group, but lacked statistical significance. Seroma aspiration within 30 d is performed at a higher rate than described in other studies (21.5−37%), which can be explained by the relatively short period the surgical drain is left in place according to our hospital protocol [15–17].

Duration of surgery was assessed in this study and used as a measure of technical difficulty of the operation. Naturally, there are various factors of influence on the duration of surgery, such as the type of dissection, anatomical variation and experience of the surgeon. There was a non-significant difference in duration of surgery for the neoadjuvant group, which was longer for the neck and groin dissections. One concern regarding neoadjuvant therapy is that delay of surgery might lead to increasingly difficult resections, either by tumour progression or fibrotic tissue changes. This matter is also addressed in a study by Hieken et al., who studied the difficulty of surgery by assessment of the surgeon in a survey. In this study lymphadenectomy for stage III melanoma was more frequently perceived to be easier after neoadjuvant therapy than perceived at baseline [8]. However, in this study, targeted therapy was used instead of ICI as neoadjuvant systemic therapy, which is known to improve operability [19].

To our knowledge, this is the first study to describe textbook outcomes for lymph node dissections in melanoma. It takes into account several aspects that are of importance for the qualitative outcomes of the surgery for stage III melanoma. This study shows that the perioperative surgical outcomes are comparable for patients who receive neoadjuvant systemic treatment with ICI and upfront therapeutic lymph node dissection in this small retrospective single institution cohort. This information supports the notion that neoadjuvant systemic therapy can be safely implemented in the care for stage III melanoma.

Although this is the first study to compare the surgical outcomes between these groups, this data must be interpreted with caution. Firstly, the number of patients included in this study was small, as it was a single-centre study. Secondly, this study only included patients who received anti-PD1 and anti-CTLA-4 therapy; it does not provide information about the outcomes after single-agent anti-PD-1 or neoadjuvant targeted therapy. Thirdly, in both neoadjuvant trials, patients were treated with ICI therapy within 6 weeks prior to surgery. Perhaps longer neoadjuvant treatment, or a longer interval between systemic treatment and surgery, could have a different influence on the surgical outcomes. Furthermore, patients who are included in a clinical trial are assessed more strictly, which could cause complications to be noticed earlier in the neoadjuvant group. However, the clinical follow-up in the first 90 d postoperatively was the same for both groups in this study. Finally, the groups were heterogenous and there were differences in baseline characteristics. The neoadjuvant

group was significantly younger, had a lower nodal tumour burden and more often had a SLNB prior to lymph node dissection in the same nodal basin, which could also have influenced our results. A multivariate subgroup analysis to correct this was not performed because of the small number of patients included. Prospective assessment of technical difficulty of surgery, reporting of complications and duration of surgery will validate or refute these findings in the future.

5. Conclusion

This study shows that surgical outcomes are comparable for patients who underwent a lymph node dissection after neoadjuvant systemic immunotherapy or underwent upfront lymph node dissection for high-risk stage III melanoma. Prospective assessment of technical difficulty of surgery, reporting of complications and duration of surgery will validate or refute these findings in the future.

Author contributions

Lisanne P. Zijlker, MD; Conceptualization, Investigation, Data curation, Writing - Original Draft. Stijn van der Burg, MD; Data curation, Writing - Original Draft. Charlotte L. Zuur MD, PhD; Review & editing. W. Martin C. Klop MD, PhD; Review & editing. Christian U. Blank MD, PhD; Review & editing. Michel W.J.M. Wouters, MD, PhD; Review & editing. Winan J. van Houdt, MD, PhD; Conceptualization, Supervision, Review & editing. Alexander C.J. van Akkooi, MD, PhD; Conceptualization, Supervision, Review & editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AvA declares to have received advisory Board & Consultancy Honoraria: Amgen, Bristol-Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Provectus, Sanofi, Sirius Medical, 4SC. Research Grants: Amgen, Merck-Pfizer. MW declares a research grant received from Novartis. WvH declares to have received advisory Board & Consultancy Honoraria for Amgen, Belpharma, Novartis, MSD-Merck, Sanofi. All unrelated to the current work under consideration. All remaining authors have declared no conflicts of interest.

Appendix

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
- IIIa	Intervention not under general anaesthesia.
- IIIb	Intervention under general anaesthesia.
Grade IV	Life-threatening complications (including CNS complications) requiring IC/ICU-management.
- IVa	Single organ dysfunction (including dialysis).
- IVb	Multiorgan dysfunction.
Grade V	Death of a patient.

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