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The Type of Surgical Axillary Staging Following Neoadjuvant Systemic Treatment Has No Impact on Breast Cancer Patients' Oncological Outcomes

Ana Car Peterko*[a], Manuela Avirović[b], Petra Valković Zujić[c], Damir Grebić[a], Damir Juranić[d], Franjo Lovasić[a]

[a]*Department of General Surgery and Surgical Oncology, Clinical Hospital Centre Rijeka, Rijeka, Croatia*

[b]*Department of Pathology, University of Rijeka, Faculty of Medicine, Rijeka, Croatia*

[c]*Clinical Department of Radiology, Clinical Hospital Centre Rijeka, Rijeka, Croatia*

[d]*Department of Plastic and Reconstructive Surgery, Clinical Hospital Centre Rijeka, Rijeka, Croatia*

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ABSTRACT

Background: Although response-adjusted surgery is a highly recommended strategy following neoadjuvant systemic treatment (NAST), consensus on axillary management in cN+/ycN0 breast cancer patients is still lacking. In this setting, clinical significance of the higher false negative rate of sentinel lymph node biopsy (SLNB) procedure is unknown. The present analysis aims to evaluate the long-term safety of the SLNB in ycN0 patients.

Methods: In this study, 60 patients with the operable breast cancer, undergoing surgery after NAST in Clinical Hospital Centre Rijeka, Croatia, from May 2016 to May 2018, were included in the analysis. Following a preliminary retrospective analysis in 2019, follow-up (FU) was extended, and all outcomes were re-evaluated in December 2022.

Results: The median FU time was 65 months and 98% of patients had complete FU data. In the ypN0 group, ALND was performed for 15 and SLNB for 20 patients. The median number of LN retrieved in ALND and SLNB was 15 and 3, respectively. The method of surgical axillary staging had no impact on oncological outcomes; Regional Recurrence Free Survival Chi-square=0.5789, P=0.4467; Distant Recurrence Free Survival Chi-square=1.3658, p=0.2425; Breast Cancer Specific Survival Chi-square=0.9755, P=0.3233.

Conclusion: Irrespective of a higher FNR following NAST, as compared to the upfront surgery setting, SLNB is a safe procedure and should be considered for all ycN0 patients, regardless of pre-treatment cN status.

INTRODUCTION

The pathological nodal status (pN, ypN) is one of the most important prognosticators in breast cancer, guiding the adjuvant treatment recommendations for radiation and medical oncologists. Axillary staging is, therefore, an integral part of breast cancer surgery. Historically, it has implied axillary lymph node dissection (ALND) i.e., surgical removal of all lymph nodes in the ipsilateral armpit. Until the late seventies,

***Address for correspondence:**
Ana Car Peterko
Department of General Surgery and Surgical Oncology, Clinical Hospital Centre Rijeka, Krešimirova 42, 51000 Rijeka, Croatia
Tel: +3851658120
Email: anacarpeterko@gmail.com

the procedure was considered therapeutic for all breast cancer patients and was performed in all patients irrespective of the stage of the disease, regardless of the high morbidity and complication rates related to the procedure. Following National Surgical Adjuvant Breast and Bowel Project (NASBP) B-04 trial results[1,2] a new staging procedure had to be invented for the early-stage breast cancer patients, as the results did not confirm any therapeutic impact of axillary clearance in this patient's cohort. Sentinel lymph node biopsy (SLNB) has emerged as a potential alternative procedure. Following several validation trials[3-6] it was widely accepted as a standard of care in early-stage breast cancer surgical nodal staging. Further trials[7-13] have confirmed that ALND can be safely omitted also in patients with the metastatic involvement of sentinel lymph node(s) and that nodal irradiation can be an equally effective alternative with a significantly lower complication rate. Although these trials have reported that axillary disease will be left behind in up to 40% of these patients, it has not been associated with any adverse impact on oncological outcomes.

At the same time in the post-NAST setting many surgeons still routinely perform standard level I-II ALND for staging purposes in many post-NAST patients, particularly those diagnosed with nodal metastasis, irrespective of axillary response to NAST.[29] Although response-adjusted surgery is highly recommended following NAST and SLNB is accepted in all relevant treatment recommendations guidelines[14,15] as a valid staging procedure in the post-NAST setting, there are still concerns about its oncological safety. It is mainly due to its higher false negative rate (FNR) determined in the early post-NAST SLNB-validation trials[16-24], particularly in the cN+ cohort. However, the FNR of 10% is an arbitrarily chosen safety border, and the clinical impact of higher values is unknown. So far, the literature reports on the oncological outcomes of patients, stratified according to axillary staging procedure after NAST, do not suggest any adverse impact of SLNB.[25-28]

This paper aims to evaluate the long-term safety of the SLNB procedure following NAST in ycN0 patients. For that purpose, the updated, 5-year follow-up on oncological outcomes of the first cohort of patients with SLNB procedure performed in the post-NAST setting in our institution was compared to the outcomes of the last ALND cohort in the same setting.

METHODS

At Clinical Hospital Centre Rijeka, Croatia, the SLNB procedure for cN+/ycN0 patients following NAST was accepted in routine clinical practice in May 2017. Overall, 95 female breast cancer patients underwent surgery following NAST in Clinical Hospital Centre Rijeka, from May 2016 until May 2018. However, 30 patients were excluded due to recurrent, bilateral, and metastatic disease for the preliminary, short-term FU analysis. [27, 28] For the purposes of the present analysis, additional 4 patients were excluded as both SLNB and ALND were performed, and 1 patient was lost in FU. Thereby, 60 patients were included in the present retrospective analysis.

We have defined cN+ status as clinically and/or radiologically suspicious axillary lymph node(s) at the time of diagnosis, detected by palpation and/or axillary ultrasound (AUS) and/or magnetic resonance imaging (MRI). Cytological or histological confirmation of nodal involvement before NAST was not mandatory.

AC-T protocol,[Doxorubicin hydrochloride (Adriamycin) and cyclophosphamide, followed by treatment with paclitaxel] along with HER-2 blockage for HER-2 enriched tumours, was administered to all patients prior to surgery.

The basis of sentinel lymph node(s) detection was 99mTc-labeled nano colloid (Nanocoll®) detected intraoperatively with a handheld gamma detecting probe (Neoprobe® Gamma Detecting System). Dual tracer and targeted axillary dissection (TAD) were not obligatory according to our institutional protocol at that period. All removed sentinel lymph nodes were intraoperative longitudinally transacted on 4 mm cuts and analyzed by imprint cytology. For all positive or suspected cases, cuts were frozen and histologically examined for the presence or absence of metastasis. Sentinel lymph nodes negative on imprint cytology were transacted afterwards for haematoxylin and eosin and pan-cytokeratin staining. Therefore, the detection of every residual tumor in the lymph node, including isolated tumor cells (ITC), was ensured. To stage the primary tumor and lymph nodes, we used the 4th edition of the World Health Organization (WHO) TNM classification form 2012 and the appendix of the American Joint Committee of Cancer (AJCC) manual for breast cancer staging. Therefore, ypN+ status is defined as any tumor cell detected in harvested axillary lymph node(s), including ITC.

The axillary conversion rate was calculated as the cN+/ypN0 ratio.

For all cN(+) and yp(N+) patients, adjuvant nodal irradiation was performed on therapeutic machine Siemens Oncor Expression, according to the institutional protocol in that time period. The total dose of 50 Gy was administrated in 2.0 Gy daily fractions. For all node-positive patients in whom ALND was omitted due to axillary conversion following NAT as well as for all ypN2-3 patients, the irradiation field included the first, second and third

axillary levels, the interpectoral region and the supraclavicular region. The first and second axillary levels were excluded in ypN0-1 cases in whom ALND was performed. For that time, the 2D technique was utilised for nodal irradiation in our institution. Single, anterior field was designed according to the following boundaries: thyrocricoid groove (cranial), 1 cm across medial border of sternocleidomastoid muscle (medial), medial to the humeral head and insertion of deltoid muscle (lateral), below clavicle head (caudal). Field is angled approximately 10 to 15 degrees laterally to spare the cervical spine. Dose is calculated at a depth of 3 cm.

The preliminary, short-term follow-up (FU) results were reported in 2020. [27, 28] Patients were followed thereafter per the institutional protocol and the outcomes were re-assessed in December 2022.

FU time is expressed as the number of months from the date of diagnosis until the date of the last clinical control. The median FU time of our cohort was 64.5 (10-92) months.

The oncological outcomes are defined as follows: locoregional recurrence (LR) as ipsilateral invasive in breast recurrence, regional recurrence (RR) as ipsilateral axillary, internal mammary or supraclavicular lymph node(s) recurrence, locoregional recurrence (LRR) as any ipsilateral or contralateral local or regional recurrence, distant recurrence (DR) as metastatic disease detected in any site except for regional lymph nodes and breast cancer-specific mortality (BCSM) as death caused by breast cancer. Time to recurrence/death was expressed as the number of months from the date of diagnosis until the date of the recurrence/death. Recurrence-free survival/breast cancer-specific survival was expressed as the number of months from the date of diagnosis until the confirmation of the recurrence of interest or death caused by breast cancer or until the date of last clinical control in cases without recurrence/death.

The primary endpoint of this analysis was to evaluate regional, local, and distant recurrence rates and breast cancer-specific survival rates in a cohort of breast cancer patients with ypN0 status in correlation with the extension of surgical procedure in the axilla (ALND vs. SLNB), i.e., to evaluate the safety of the SLNB procedure in the post-NAST setting.

The secondary endpoint was to evaluate the prognostic significance of the axillary involvement at diagnosis (cN+ status) vs. following NAST (ypN+), i.e., to evaluate the prognostic significance of axillary response to NAST. For that purpose, we compared all oncological outcomes among a group of patients that achieved a complete axillary response (cN+/ypN0) and the group of patients that did not (cN+/ypN+), irrespective of the axillary procedure performed.

In addition, the rates of axillary seromas that required repeated aspirations and the ipsilateral arm lymphoedema rates were compared between SLNB and ALND cohorts.

All data required for this analysis were retrospectively extracted from the integrated hospital informatics system, following the written approval of the institutional Ethics Committee. Due to the retrospective nature of the study, informed consent of the patients was not required because the study analyzed anonymous clinical data of the patients.

MedCalc® Statistical Software version 20.210 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) was used for the statistical analysis. The proportion difference test was used for the comparison of the baseline characteristics of SLNB and ALND cohorts, as well as for the comparison of axillary seroma and ipsilateral lymphoedema rates among these cohorts. All survival curves were calculated with the Kaplan-Meier method and compared with the Logrank test. The results were considered statistically significant at $P<0.05$.

RESULTS

Overall, 60 patients were included in the study. The average age at the time of diagnosis was 55 (25-78) years and 98% of patients had complete FU data.

SLNB was performed as a single staging procedure for 20 patients and ALND for 40 patients. The average number of lymph nodes harvested per procedure was 3 (1-6) in SLNB and 15 (6-26) in ALND.

The axillary conversion rate, cN+/ypN0, was 34%.

The overall study cohort characteristics and the subgroups stratified by the type of axillary procedure are displayed in Table 1.

The survival analysis has been performed in 3 subgroups of patients.

Survival analysis for all ypN0, irrespective of cN status, stratified by the extent of axillary surgery (ALND vs. SLNB), has not shown any statistically significant difference in local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), locoregional recurrence-free survival (LRRFS), distant recurrence-free survival (DRFS) and breast cancer-specific survival (BCSS), as shown in Figure 1 (a-e).

Survival analysis for cN+/ypN0 patients, stratified by the extent of axillary surgery (ALND vs. SLNB), has not shown any statistically significant difference in LRFS, RRFS, LRRFS, DRFS, event-free survival (EFS) and BCSS, as indicated in Figure 2 (a-f).

Table 1. Study cohort characteristics

Type of axillary procedure	overall	SLNB only	ALND only	ALND vs SLNB proportion difference test p-value
Number of patients	60	20	40	
HR+ disease	48 (80%)	17 (85%)	29 (73%)	0.7
HR- disease	14 (23%)	3 (15%)	11 (27%)	0.389
HER2+ disease	22 (37%)	8 (40%)	14 (35%)	0.799
HER2- disease	38 (63%)	12 (60%)	26 (65%)	0.858
<50 years at diagnosis	20 (33%)	8 (4o%)	12 (30%)	0.591
>50 years at diagnosis	40 (67%)	12 (60%)	28 (70%)	0.728
Surgery before May 2017	20 (33%)	3 (15%)	17 (43%)	0.119
Surgery after May 2017	40 (67%)	17 (85%)	23 (57%)	0.355
ypT0	13 (22%)	7 (35%)	6 (15%)	0.168
ypT1	27 (4.5%)	10 (50%)	17 (42.5%)	0.738
ypT2	10 (17%)	3 (15%)	7 (17.5%)	0.837
ypT3	5 (8%)	-	5 (12.5%)	-
ypT4	5 (8%)	-	5 (12.5%)	-
cN(-) disease	13 (22%)	11 (55%)	2 (5%)	<0.001
cN(+) disease	47 (78%)	9 (45%)	38 (95%)	0.103
ypN0	35 (58%)	20 (100%)	15 (37.5%)	0.024
ypN1	8 (13%)	-	8 (20%)	-
ypN2	12 (20%)	-	12 (30%)	-
ypN3	5 (8%)	-	5 (12.5%)	-
cN(-)/ypN0	13 (22%)	11 (55%)	2 (5%)	<0.001
cN(-)/ypN1-3 (excluded)	-	-	-	-
cN(+)/ypN0 (axillary conversion rate)	22 (37%)	9 (45%)	13 (32.5%)	0.528
cN(+)/ypN1-3	25 (42%)	-	25 (62.5%)	-
Regional recurrence (RR)	6 (10%)	1 (5%)	5 (12.5%)	0.407
Median time to RR/months	32	36	28	
Local recurrence (LR)	6 (10%)	0 (0%)	6 (15%)	0.093
Median time to LR/months	23	-	18	
Distant recurrence (DR)	22 (37%)	3 (15%)	18 (45%)	0.098
Median time to DR/months	23	36	20	
Breast cancer-specific mortality (BCSM)	19 (32%)	3 (15%)	16 (40%)	0.145
Median time to BCSM/months	32	49	32	
Lymph nodes retrieved (median)	11	3	15	
Axillary seroma	17 (28%)	1 (5%)	16 (40%)	0.026
Ipsilateral arm lymphedema	9 (15%)	1 (5%)	8 (20%)	0.179

HR=hormone receptor, HER2= epidermal growth factor receptor 2, ypT=post-NAST pathological tumour status, cN=clinical nodal status at diagnosis, ypN=post-NAST pathological nodal status.

Survival analysis for cN+ patients, stratified by the axillary response to NAST (cN+/ypN0 vs. cN+/ypN+), has not shown any statistically significant difference in LRFS, RRFS, LRRFS, DRFS, EFS and BCSS, as shown in Figure 3(a-f).

Early and late postoperative complication rates related to the type of axillary procedure are displayed in Figure 4.

DISCUSSION

Our breast cancer study cohort was composed of patients submitted to surgery following NAST one year before and one year after SLNB was accepted as a staging procedure for cN+/ycN0 patients in our institution in May 2017. Thereby, all patients were treated per equal recommendations, except for the axillary surgical staging. Following 5-year follow-up, all oncological outcomes were assessed, and the survival analysis was performed, stratified by the type of axillary procedure. There was no clinically meaningful or statistically significant difference observed in LRFS, RRFS, LRRFS, DRFS and BCSS associated with the type of axillary procedure performed after NAST in ypN0 patients, irrespective of the clinical nodal status at the time of diagnosis. Overlapping survival curves imply that SLNB is an oncological safe procedure for axillary staging after NAST in all ycN0 patients, associated with significantly lower complication rates and postoperative morbidity as compared to ALND. These observations are concordant with previous literature reports[25-28] and support the clinical practice guidelines recommending SLNB as the preferred option for axillary staging in the post-NAST setting since 2017.[14,15]

However, in routine clinical practice, the procedure is still not a universally accepted standard of care. According to the results of an international European Breast Cancer Research Association of Surgical Trial list (EUBREAST) web-based survey of axillary management in cN+/ycN0 patients, conducted among 345 breast surgeons from 43 countries in 2021, standard ALND (level I-II) was still a preferred option in 19% of responders.[29]

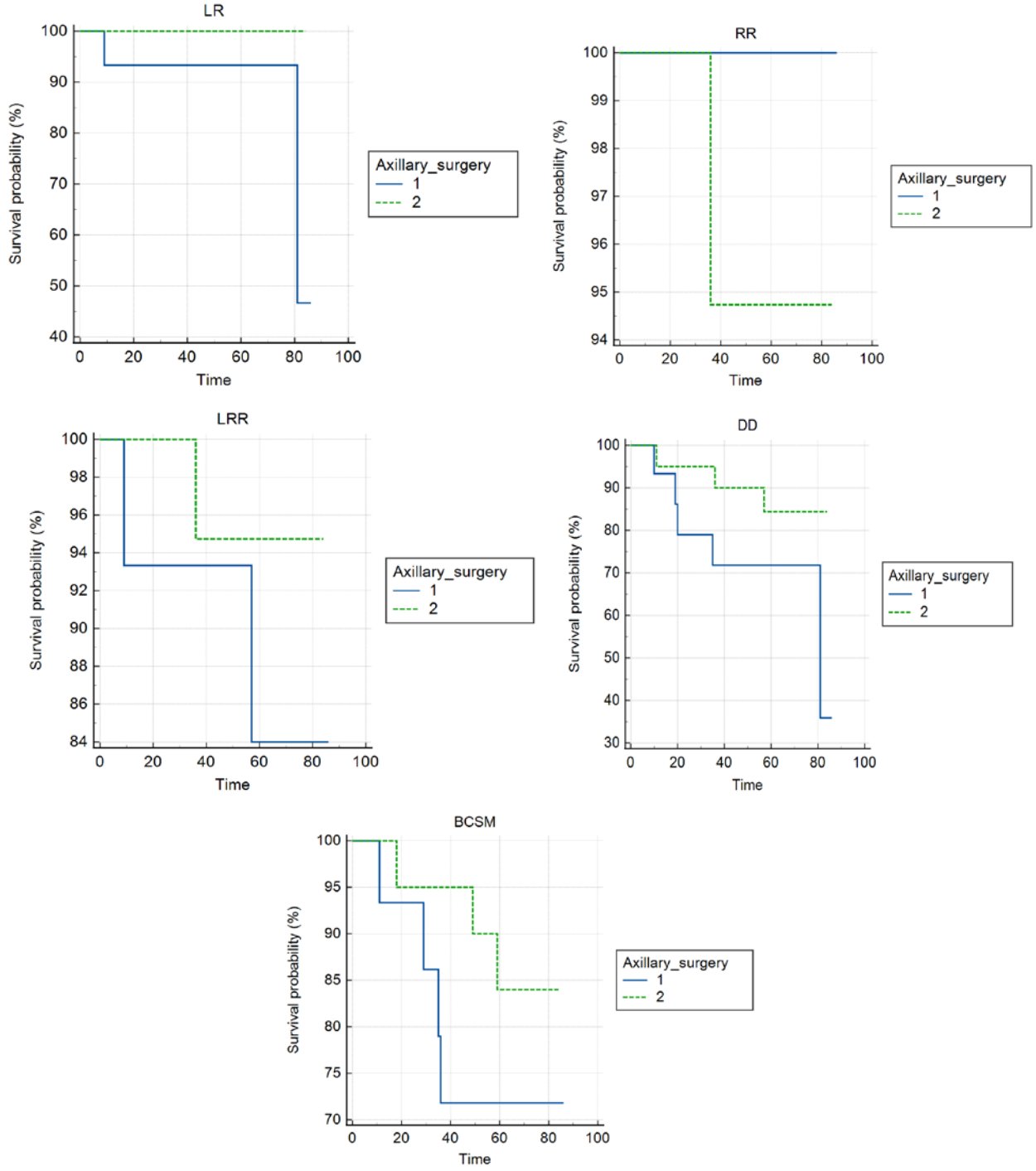

Figure 1.a. Local recurrence-free survival (LRFS) in the ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 86.67% vs. 100%, Chi-square 1.7524, P=0.1856). **b.** Regional recurrence-free survival (RRFS) in the ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 100% vs. 95%, Chi-square=0.5789, P=0.4467). **c**. Locoregional recurrence-free survival (LRRFS) in the ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 86.67% vs. 95%, Chi-square=1.0020, P=0.3168). **d.** Distant recurrence-free survival (DRFS) in the ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 66.67% vs. 85%, Chi-square=1.3658, P=0.2425). **e.** Breast cancer-specific survival (BCSS) in the ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 73.3% vs. 85%, Chi-square=0.9755, P=0.3233)

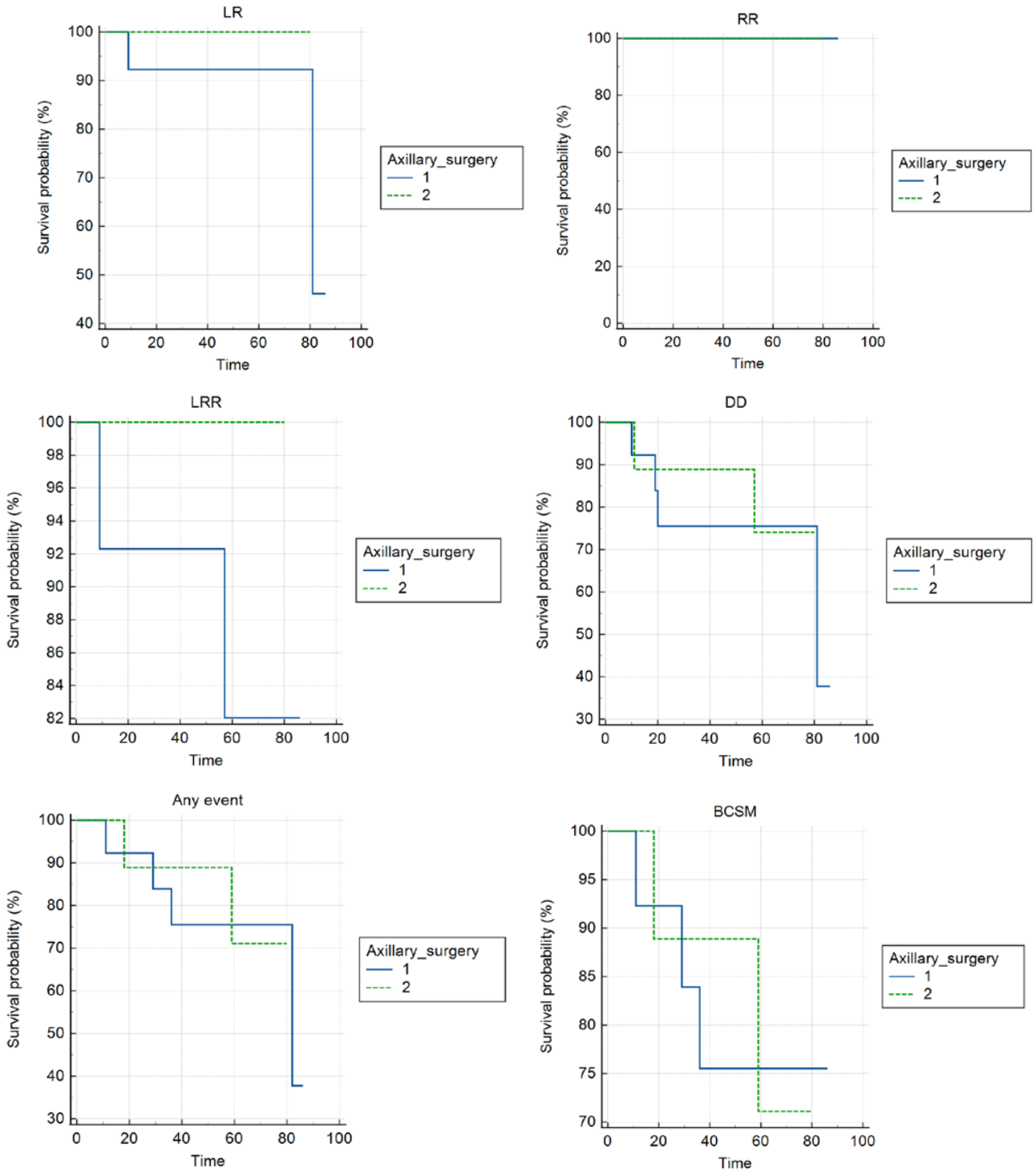

Figure 2.a. Local recurrence-free survival (LRFS) in the cN+/ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 84.62% vs. 100%, Chi-square=0.6923, P=0.4054). **b.** Regional recurrence-free survival (RRFS) in the cN+/ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 100% vs. 100%). **c.** Locoregional recurrence-free survival (LRRFS) in the cN+/ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 86.62% vs. 100%, Chi-square=1.3589, P=0.2437). **d.** Distant recurrence-free survival (DRFS) in the cN+/ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 69.23% vs. 77.78%, Chi-square=0.005523, P=0.9252). **e.** Event-free survival (EFS) in the cN+/ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 69.23% vs. 77.78%, Chi-square=0.005523, P=0.9408). **f.** Breast cancer-specific survival (BCSS) in the cN+/ypN0 subgroup, according to axillary procedure (1=ALND vs. 2=SLNB; 76.92% vs. 77.78%, Chi-square= 0.005523, P=0.9408)

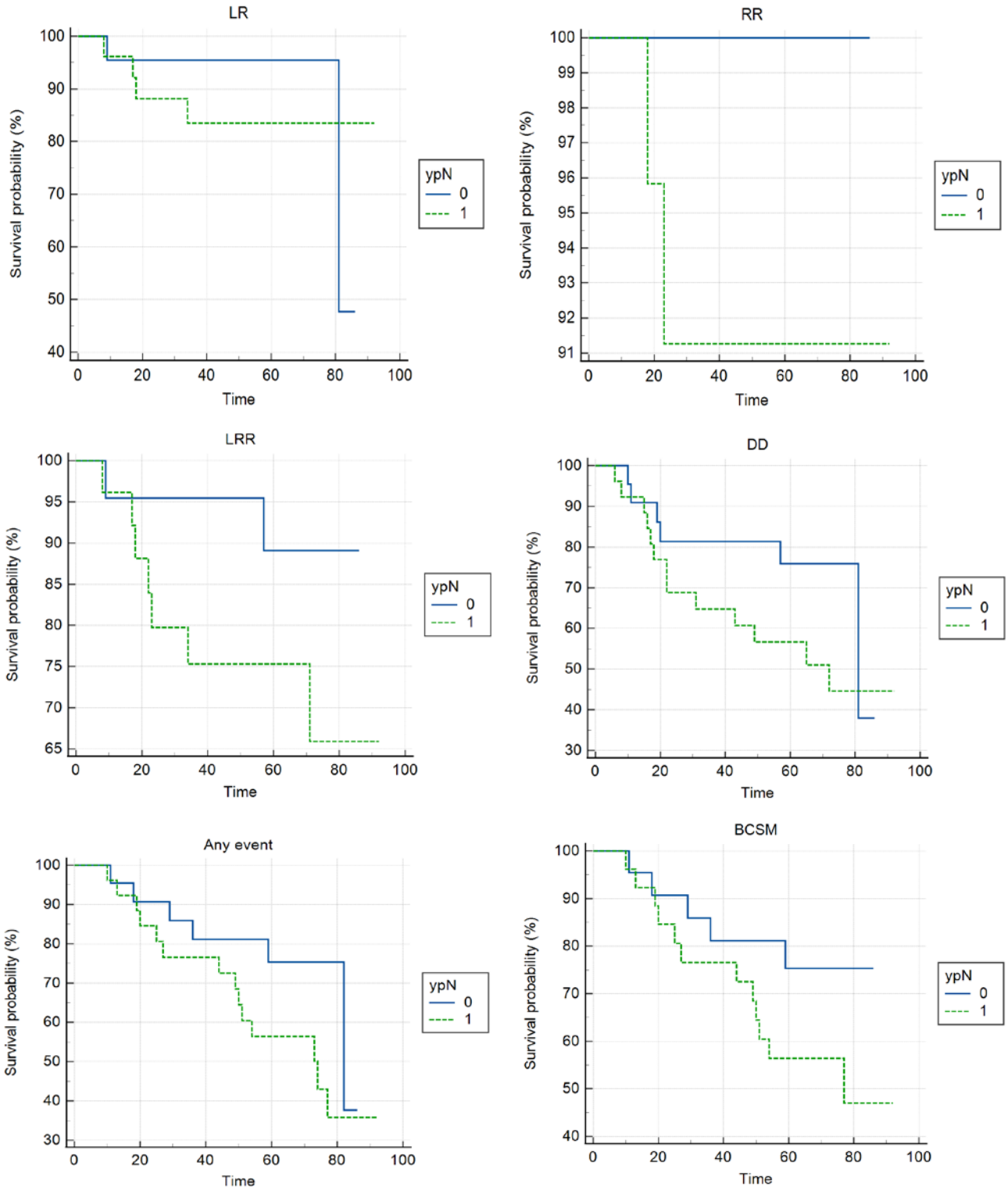

Figure 3.a. Local recurrence-free survival (LRFS) according to axillary response to NAST (0=cN+/ypN0 vs. +=cN+/ypN+; 90.91% vs. 84.62%, Chi-square=0.4217, P=0.5161). **b.** Regional recurrence-free survival (RRFS) according to axillary response to NAST (0=cN+/ypN0 vs. +=cN+/ypN+; 100% vs. 92.31%, Chi-square=1.7375, P=0.1875). **c.** Locoregional recurrence-free survival (LRRFS) according to axillary response to NAST (0=cN+/ypN0 vs. +=cN+/ypN+; 90.91% vs. 73.08%, Chi-square=2.1792, P=0.1399). **d.** Distant recurrence-free survival (DRFS) according to axillary response to NAST (0=cN+/ypN0 vs. +=cN+/ypN+; 72.73% vs. 50%, Chi-square=2.1014, P=0.1472). **e.** Event-free survival (EFS) according to axillary response to NAST (0=cN+/ypN0 vs. +=cN+/ypN+; 72.73% vs. 46.15%, Chi-square=2.0603, P=0.1512). **f.** Breast cancer-specific survival (BCFS) according to axillary response to NAST (0=cN+/ypN0 vs. +=cN+/ypN+; 77.27% vs. 53.85%, Chi-square=2.1486, P=0.1427)

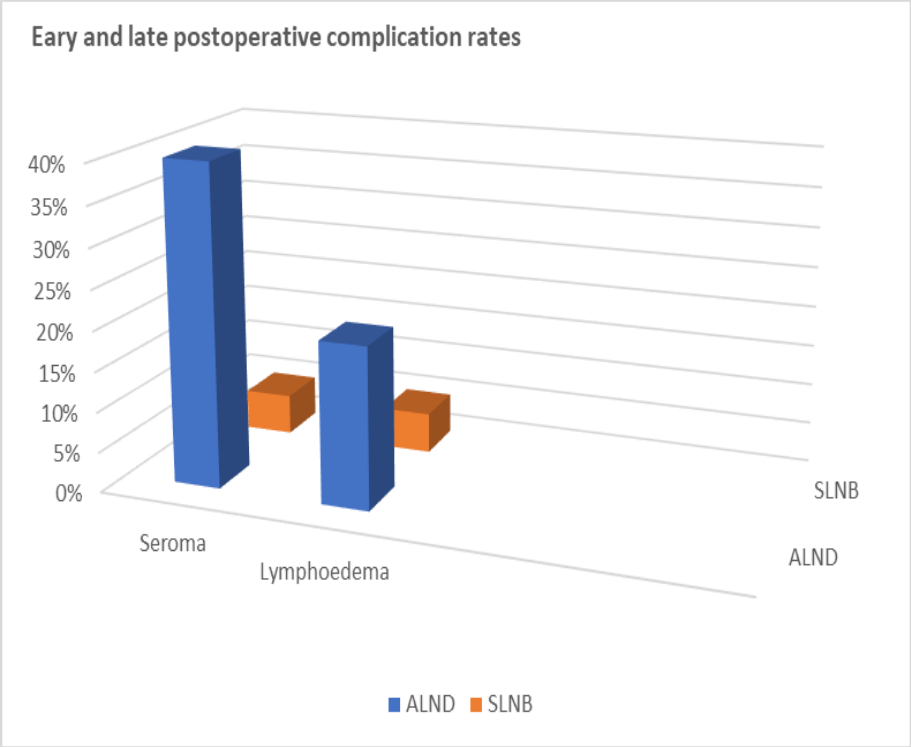

Figure 4. Axillary seroma and ipsilateral arm lymphedema rates in relation to the type of axillary procedure

This is mainly due to the higher FNR of the SLNB procedure following NAST, as compared to the FNR in the upfront surgery setting, observed in the early post-NAST SLNB validation trials [16-19] and consecutive concerns about a higher risk of undertreatment. However, the "safe" FNR is an arbitrarily chosen border and there is no scientific evidence to support that higher values would have any adverse impact on oncological outcomes. So far, literature reports [25-28], including the results presented herein, imply that post-NAST SLNB is a safe procedure of nodal staging and therefore should be considered for all ycN0 patients, irrespective of pre-treatment cN status.

In addition, in modern breast cancer management, NAST is not exclusively reserved for the advanced-stage disease. Due to imperfections in clinical axillary staging [30], many early-stage breast cancer patients, who may fulfil Z11 and/or AMAROS criteria [11, 12], may as well receive preoperative systemic treatment and consequently end up with axillary clearance merely for the nodal staging purpose, regardless of initial nodal status and the axillary response to NAST. This decision is mainly driven by concerns regarding possible under-staging and consecutive under-treatment, as well as by the fear of leaving any chemo-resistant disease behind.

Although axillary ultrasound is highly unreliable in differentiating cN0 and cN1 and may not recognise up to 50% of low-volume metastatic disease [30], it is a great tool for differentiation between low-volume and high-volume nodal involvement. As the risk of pN2-3 status in AUS-negative patients is extremely low [31], the concern about leaving a significant nodal burden following AUS and SLNB procedure is not actually an issue at all. For patients with limited nodal involvement (1-3 lymph nodes), the scientific evidence on the therapeutic impact of ALND in the post-NAST setting is lacking. Moreover, the post-NAST residual disease may not be radioresistant and nodal irradiation may represent an effective alternative. This concept has already been confirmed in several trials in the upfront surgery setting [7-13] and ongoing trials [32-34] are exploring it in the post-NAST setting.

As a prognosticator, ypN+ status suggests a worse patient outcome [29] regardless of surgical intervention in the axilla, indicating the need for adjuvant systemic treatment escalation as well as the need for adjuvant irradiation. Herein, we failed to observe any statistically significant difference in LRFS, RRFS, LRRFS, DRFS, EFS and BCSS, stratified by the axillary response to NAST (cN+/ypN0 vs. cN+/ypN+), probably due to the our small sample size. Nevertheless, the separation of DDFS, EFS and BCSS curves suggest clinically meaningful difference and imply that axillary response to NAST may be a more valuable prognosticator than initial nodal status.

The accurate determination of ypN status is obviously an important issue, as it guides the adjuvant treatment recommendations. However, the risk of undertreatment based solely on higher FNR of post-NAST SLNB procedure is very low. According to

existing guidelines, any residual disease detected in the breast or axilla following NAST mandates adjuvant systemic treatment escalation and residual nodal involvement in the case of breast pCR is a very rare event. [35, 36]

As randomization between SLNB and ALND in ycN0 patients would represent an ethical issue after 2017, a randomized control trial (RCT) that may confirm our observations is highly unlikely. Therefore, we started a prospective observational study in 2018 [37] in our institution to confirm our initial findings on a larger and prospective cohort. At the end of the 5 years of FU, the outcomes of the post-NAST SLNB cohort will be compared to the historical retrospective ALND control. [38] The results will hopefully contribute to better acceptance of the SLNB procedure and its implementation in routine clinical practice in post-NAST settings. As the axillary conversion rates are high, many patients may be safely spared from unnecessary surgery and related morbidity.

CONCLUSION

SLNB after NAST is not inferior to ALND for locoregional and overall control of the disease in ycN0 cohort. As response-adjusted surgery is highly recommended following NAST. SLNB should be a standard of care in all ycN0 patients, irrespective of nodal status at diagnosis.

Axillary response to NAST may be a more valuable prognosticator than initial nodal status. It suggests a worse patient outcome and indicates the need for adjuvant systemic treatment escalation as well as the need for adjuvant irradiation. A bigger surgery (ALND) for staging purposes does not improve oncological outcomes in ycN0 cohort and is most likely not beneficial in patients with limited residual nodal disease in the post-NAST setting. The results of ongoing prospective trials may confirm our observations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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None.

ETHICAL CONNSIDERATIONS

This research was conducted ethically following the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Clinical Hospital Centre Rijeka. Due to the retrospective nature of the study, informed consent of the patients was not required.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author.

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