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Original research article

Patterns of post-operative irradiation in breast cancer patients submitted to neoadjuvant chemotherapy

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A B S T R A C T

Background/Aim: Post-operative radiation therapy (PORT) is associated with improvement in loco-regional control and survival rates in early breast cancer. However, the evidence of benefit in patients after treatment with neoadjuvant chemotherapy (NAC) is poor. We aimed to assess the impact of the type of surgery in the PORT plan and the role of the PORT fields in clinical outcomes in breast cancer patients who had undergone NAC followed by surgery.
Materials and methods: We performed a retrospective analysis of all non-metastatic breast cancer patients treated between 2008 and 2014 at our institution who had received NAC and PORT.
Results: A total of 528 women were included of whom 396 were submitted to mastectomy or nipple-sparing/skin-sparing mastectomy. Most (92.8%) of the patients had locally advanced disease (clinical stage IIB to IIIC). All patients underwent irradiation for breast or chest wall. Most patients received PORT to the supraclavicular and axillary (levels II and III) nodes (87.1% and 86.4% for breast-conserving surgery and 95.1% and 93.8% for mastectomy and nipple-sparing/skin-sparing mastectomy, respectively). Irradiation of level I axillary and internal mammary nodes was uncommon. The disease-free survival and overall survival rates at 3 years were 72% and 85%, respectively. There were no statistically significant differences in clinical outcomes according to the use of nodal irradiation.

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Conclusions: After NAC, most patients received irradiation of the breast/chest wall and axillary and supraclavicular nodes. In this setting, PORT to breast/chest wall with or without regional nodal irradiation was safe and effective, with acceptable disease-free and overall survival rates reported in this high-risk population.

1. Background

Neoadjuvant chemotherapy (NAC) is one of the options for the management of locally advanced breast cancer patients.[1] Several prospective randomized phase III trials demonstrated equivalent overall survival (OS) rates when comparing adjuvant to NAC. Moreover, these studies confirmed superior rates of breast conservation in patients with favorable response to NAC.[2–8] Hence, over the years, the use of NAC has been growing due not only to higher rates of breast conservation, but also to a number of other potential benefits. Of note, response to NAC is a good prognostic factor, especially in Her-2 positive and triple negative, which could assist physicians in assessing the need for additional treatments.[9]

For selected patients with breast cancer, many trials showed that post-operative radiation therapy (PORT) is associated with improvement in loco-regional control and survival rates regardless of the surgery type that was performed after adjuvant chemotherapy. However, none of these studies included patients treated with NAC.[10–13] Phase III randomized trials that compared adjuvant chemotherapy to NAC did not specifically address the role of PORT – in these older trials, radiation therapy was given to the whole breast for all patients who underwent breast-conserving surgery and was usually omitted after mastectomy.[2,3] Hence, the significance of these studies in supporting PORT recommendations is low, especially after mastectomy.

The NAC approach can significantly influence radiation therapy indications after breast surgery by theoretically altering the loco-regional relapse risk according to the magnitude of response. This raises questions about the actual need for PORT therapy in more 'favorable' subsets of patients (those who achieved pCR or near-pCR) – a proposed alternative being reserving PORT to patients with gross residual tumor after NAC. In addition, there are many uncertainties about the most appropriate radiation therapy fields in patients who received NAC given that all recommendations are based on initial clinical and pathological aspects.[14,15]

The current study aimed to assess the impact of the type of surgery in the radiation therapy plan and the role of the radiation therapy fields in clinical outcomes in breast cancer patients who had undergone NAC followed by surgery.

2. Patients and methods

2.1. Study design and patient population

We performed a retrospective analysis of all non-metastatic breast cancer patients (T1-T4, N0-N3 and M0) treated between 2008 and 2014 who had received neoadjuvant chemotherapy followed by curative surgery and PORT therapy breast or chest wall with or without regional lymph node irradiation. Patients were properly staged according to institutional standards. Demographic and clinical data of patients were extracted from the medical records after approval by the local institutional review board and ethics committee.

2.2. Treatment

Surgery was performed after completion of NAC. The choice between breast-conserving surgery or mastectomy/nipple-sparing/skin-sparing mastectomy was made on a case-by-case basis. Hormone therapy was indicated for all patients with positive hormonal receptors and the NAC regimen was indicated by the treating physician as per institutional practice. All patients were treated using three-dimensional conformal radiation therapy in a linear accelerator. Data regarding treatment fields as well as delivered doses were collected.

2.3. Statistical methods

Demographics and baseline characteristics were summarized using descriptive statistics and compared using Fisher's exact test or Chi-square whenever appropriate. All time-to-event endpoints had the date of surgery as the start date. Overall (defined as the time from surgery to death of any cause) and disease-free survival (defined as the time from surgery to any recurrence event or death) were estimated using the Kaplan-Meier method with the log-rank test for comparisons between variables. Multivariable analysis was performed using the binary logistic regression model to calculate the adjusted odds ratios for recurrence. All tests were two-sided and a p value < 0.05 was considered statistically significant. SPSS software (version 20.0; SPSS, Chicago, IL, USA) and R version 3.4.3 were used for statistical analyses.

3. Results

3.1. Patient characteristics

Between January/2008 and December/2014, 523 patients underwent NAC followed by surgery and, then, adjuvant radiation therapy. The majority of the study population had locally advanced disease (92.8%) and underwent mastectomy or nipple-sparing/skin-sparing mastectomy (75%). Luminal-like, triple positive, Her-2 positive and triple negative subtypes represented 44.4%, 14.3%, 12.6%, and 28.7% of the entire cohort, respectively. Almost all patients received

Table 1 – Clinical characteristics of the patients according to the type of surgery.

	Total (N = 523)		Breast-conserving surgery (N = 132)		Mastectomy or nipple-sparing/skin-sparing mastectomy (N = 391)		*p*
	N	%	N	%	N	%	
Age at diagnosis (years)							0.12
Mean	50.9		51.8		50.0		
Range	23–84		26–84		23–77		
Clinical tumor stage[a]							<0.001
cT1	4	0.8	2	1.5	2	0.5	
cT2	130	24.6	59	44.7	71	18.2	
cT3	248	47.4	53	40.2	195	49.9	
cT4	141	27.0	18	13.6	123	31.5	
Clinical nodal stage[a]							0.02
cN0	99	18.9	36	27.3	63	16.1	
cN1	214	40.9	52	39.4	162	41.4	
cN2	162	31.0	31	23.5	131	33.5	
cN3	48	9.2	13	9.8	35	9.0	
Clinical stage[a]							<0.001
I	2	0.4	2	1.6	0	0.0	
IIA	37	7.1	19	14.4	18	4.6	
IIB	97	18.5	38	28.8	59	15.1	
IIIA	219	41.9	46	34.8	173	44.2	
IIIB	124	23.7	16	12.1	108	27.6	
IIIC	44	8.4	11	8.3	33	8.4	
Pathologic tumor stage[a] **at surgery**							<0.001
ypT0/pTis	126	24.1	42	31.8	84	21.5	
ypT1	152	29.1	48	36.4	104	26.7	
ypT2	152	29.1	40	30.3	112	28.7	
ypT3	73	14.0	2	1.5	71	18.2	
ypT4	19	3.6	0	0	19	4.9	
Pathologic nodal stage[a] **at surgery**							0.001
ypN0	254	48.8	84	63.6	170	43.8	
ypN1	158	30.4	31	23.5	127	32.7	
ypN2	69	13.3	11	8.3	58	14.9	
ypN3	39	7.5	6	4.5	33	8.5	
Estrogen receptor							0.19
Positive	304	58.1	70	53.0	234	59.8	
Negative	219	41.9	62	47.0	157	40.2	
Progesterone receptor							0.09
Positive	254	48.6	55	41.7	199	50.9	
Negative	269	51.4	77	58.3	192	49.1	
"Molecular"							0.18
Luminal-like	232	44.4	51	38.6	181	46.3	
Triple positive	75	14.3	19	14.4	56	14.3	
HER-2 positive	66	12.6	23	17.4	43	11.0	
Triple negative	150	28.7	39	29.5	111	28.4	
Neoadjuvant chemotherapy							0.22
Anthracycline-taxane	505	96.6	130	98.5	375	95.9	
Others	18	3.4	2	1.5	26	4.1	
pCR							0.004
Yes	107	20.5	39	29.5	68	17.4	
No	415	79.5	93	70.5	322	82.6	

HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response.
[a] AJCC 2010.

anthracycline-taxane based neoadjuvant chemotherapy regimen (96.6%), plus trastuzumab for Her2 positive tumors (100%). Of note, neoadjuvant pertuzumab had not been registered by the time the study was performed. Pathologic complete response (pCR), defined as the absence of tumor in the surgical specimen (ypT0 ypN0), was observed in 20.5% of patients (Table 1).

3.2. *Radiation approach*

Radiation therapy was used for all patients regardless of surgery type or pathologic response to neoadjuvant chemotherapy. Radiation therapy features are described in Fig. 1 and Table 2. All patients underwent irradiation of the breast or chest wall.

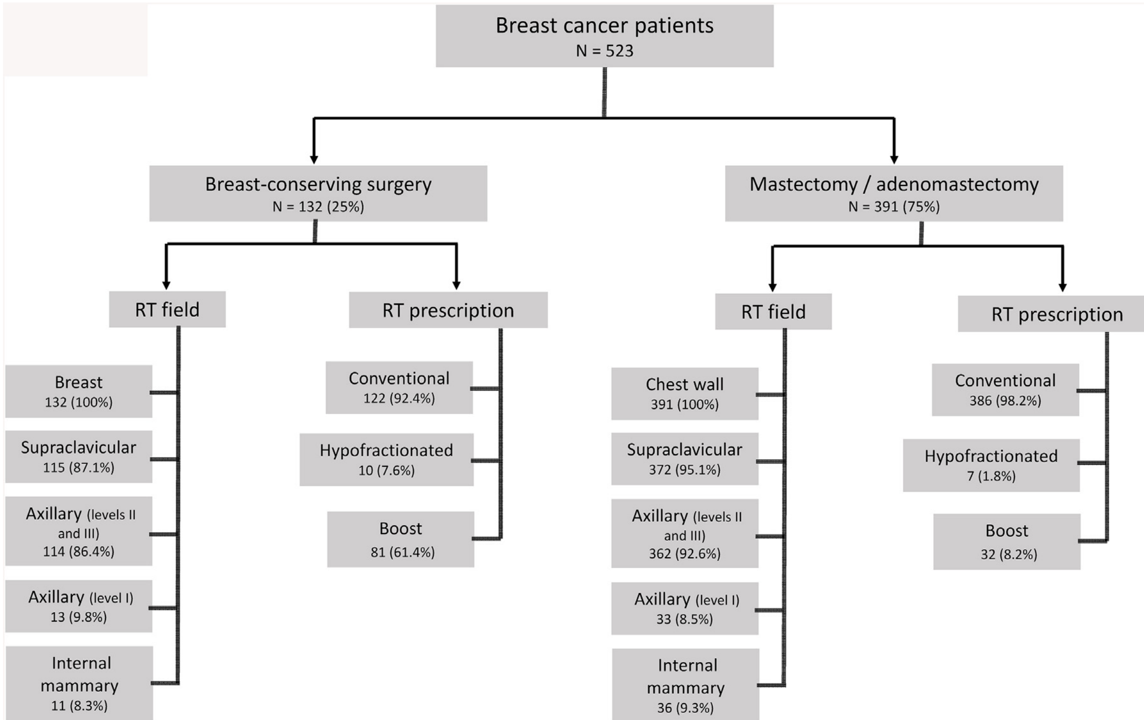

Fig. 1 – Radiation therapy features.

The most common radiation therapy schedule was the conventional 50–50.4 Gy in 25–28 fractions. Hypofractionated irradiation schedule with doses of 40.05–42.5 Gy delivered in 15–16 fractions was used in only 3.2%, especially in mastectomy/nipple-sparing/skin-sparing mastectomy patients due to the patients' difficulties in attending the service for 5 weeks to receive the conventional radiation therapy regimen. Boost was used in most (61.4%) of the breast-conserving surgery patients and in only 8.2% of mastectomy/nipple-sparing/skin-sparing mastectomy patients in the chest wall or reconstructed breast (Table 2). Our institutional protocol advocates the indication of boost mainly

Table 2 – Radiation therapy targets according to surgical approach.

Radiotherapy targets	Total (N = 523)		Breast-conserving surgery (N = 132)		Mastectomy or nipple-sparing/skin-sparing mastectomy (N = 391)		*p*
	N	%	N	%	N	%	
Breast or Chest wall							
Yes	523	100	132	100	391	100	
Supraclavicular							0.003
Yes	487	93.1	115	87.1	372	95.1	
No	36	6.9	17	12.9	19	4.9	
Axillary (levels II and III)							0.01
Yes	476	91.0	114	86.4	362	92.6	
No	47	9.0	18	13.6	29	7.4	
Axillary (level I)							0.72
Yes	46	8.9	13	9.8	33	8.5	
No	473	91.1	119	90.2	354	91.5	
Internal mammary							0.86
Yes	47	9.0	11	8.3	36	9.3	
No	474	91.0	121	91.7	353	90.7	
Dose							0.003
Conventional	506	96.7	122	92.4	384	98.2	
Hypofractionated	17	3.3	10	7.6	7	1.8	
Boost							<0.001
Yes	113	21.6	81	61.4	32	8.2	
No	410	78.4	51	38.6	359	91.8	

Table 3 – Tumor features and regional lymph node irradiation.

Characteristic	Regional lymph node irradiation				p
	Yes (487)		No (37)		
	No	%	No	%	
Clinical tumor stage					0.01
cT1	3	0.6	1	2.7	
cT2	115	23.6	15	40.5	
cT3	232	47.6	17	45.9	
cT4	137	28.1	4	10.8	
Clinical nodal stage					<0.001
cN0	77	15.8	22	59.5	
cN1	206	42.3	9	24.3	
cN2	159	32.6	3	8.1	
cN3	45	9.2	3	8.1	
Clinical stage					<0.001
I	0	0.0	1	2.7	
IIA	24	4.9	13	35.1	
IIB	89	18.3	8	21.6	
IIIA	212	43.5	8	21.6	
IIIB	120	24.6	4	10.8	
IIIC	41	8.4	3	8.1	
Pathologic tumor stage					0.65
ypT0/ypTis	119	24.5	8	21.6	
ypT1	138	28.4	14	37.8	
ypT2	142	29.2	10	27.0	
ypT3	70	14.4	3	8.1	
ypT4	17	3.5	2	5.4	
Pathologic nodal stage					<0.001
ypN0	221	45.7	34	91.9	
ypN1	156	32.2	2	5.4	
ypN2	68	14.0	1	2.7	
ypN3	39	8.1	0	0.0	
Histological grade					1.00
1	36	7.4	3	8.1	
2	207	42.6	16	43.2	
3	243	50.0	18	48.6	
"Molecular"					0.25
Luminal	219	45.0	13	35.1	
Triple positive	72	14.8	3	8.1	
HER-2 positive	60	12.3	6	16.2	
Triple negative	136	27.9	15	40.5	
pCR					1.00
Yes	100	20.6	8	21.6	
No	387	79.4	29	78.4	
Type of surgery					0.003
Mastectomy or nipple-sparing/skin-sparing mastectomy	372	76.4	19	52.8	
Breast-conserving surgery	115	23.6	17	47.2	
Axilary dissection					<0.001
Yes	455	93.4	22	59.5	
No	32	6.6	15	40.5	

to young patients (younger than 50–55 years) after conservative surgery and/or tumor grade 3. In patients who received mastectomy/nipple-sparing/skin-sparing mastectomy, boost is performed in exceptional situations, such as positive surgical margins.

3.3. *Regional lymph node irradiation*

Most of the patients received radiation therapy of the supraclavicular and axillary (levels II and III) nodes (87.1% and 86.4%; 95.1% and 93.8%, for breast-conserving surgery and mastectomy/nipple-sparing/skin-sparing mastectomy, respectively). Radiation therapy of supraclavicular nodes ($p = 0.003$) and levels II and III axillary nodes ($p = 0.01$) was statistically significantly more frequent in patients who had undergone mastectomy/nipple-sparing/skin-sparing mastectomy. Irradiation of level I axillary and internal mammary nodes was uncommon and did not diverge by surgical approach. Almost all patients with clinical stage IIB to IIIC received regional lymph node irradiation (Table 3). It is important to highlight that the axillary (level I) was normally irradiated when the axillary resection removed less than 10 lymph nodes. Internal mammary region was normally irradiated in the presence of ≥cN2 or more than 4 positive axillary lymph nodes when heart and lung constraints could be accomplished. The tumor characteristics related to regional

Table 4 – Recurrence outcomes by surgical approach.

Recurrence	TOTAL (N = 523)		Breast-conserving surgery (N= 132)		Mastectomy or nipple-sparing/skin-sparing mastectomy (N= 391)		p
	N	%	N	%	N	%	
Any recurrence							0.001
Yes	136	26.0	20	15.2	116	29.7	
No	387	74.0	112	84.8	275	70.3	
Local and/or regional							0.42
Yes	55	10.5	11	8.3	44	11.3	
No	468	89.5	121	91.7	347	88.7	
Distant							<0.001
Yes	130	24.9	18	13.6	112	28.6	
No	393	75.1	114	86.4	279	71.4	

lymph node irradiation indications were clinical stage, pathological nodal stage, type of surgery and axillary dissection status (Table 3).

3.4. *Clinical outcomes*

Recurrence outcomes by surgical approach is shown in Table 4. There were no statistically significant differences in local and/or regional recurrence rates between patients who had received breast-conserving surgery or mastectomy/nipple-sparing/skin-sparing mastectomy (8.3% versus 11.4%; $p = 0.42$). However, distant recurrence was more frequent in mastectomy/nipple-sparing/skin-sparing mastectomy patients (13.6% versus 29.0%; $p < 0.001$). Distant recurrence remained more frequent in patients who had undergone mastectomy (OR = 1.89, 95%CI 1.06–3.32, $p = 0.014$) after adjusting for pCR and clinical stage (Supplemental figure* 1).

The multivariable analysis looking at the impact of presenting surgery (non BCS versus BCS), stage (II versus III), receptor subtype, age, response to systemic treatment on the risk of recurrences (local recurrence, distant recurrence and any recurrence) were demonstrated in Supplemental Figures 2, 3 and 4). No pCR and triple negative type were related to higher local recurrence. The variables associated with less distant recurrence were breast-conserving surgery, pCR and stage I or II.

For all patients, the disease-free survival (DFS) and overall survival (OS) rates at 3 years were 72% and 85%, respectively (Figs. 2 and 3). There were no differences in survival outcomes according to nodal irradiation fields in an unadjusted exploratory analysis (Supplemental table* 1 and Supplemental Figures 5, 6 and 7).

4. Discussion

Neoadjuvant chemotherapy strategy for breast cancer patients has raised discussions on the appropriate use of PORT. Evidence for PORT comes from many trials where the treatment protocol involved surgery followed by adjuvant chemotherapy. The absence of clear indications in the subset of patients treated with NAC has led to divergent judgments about the significant features that should guide the clinical assessment whether to perform PORT or not.[16]

Although some guidelines recommended PORT for patients with advanced breast cancer who had received NAC, a lack of standardization with significant discrepancies in clinical practices is observed in this scenario worldwide.[17,18]

Although available phase III trials that compared adjuvant chemotherapy to NAC have not properly evaluated the role of the PORT approach, it is important to recognize that the data from these trials at least indicated that breast conservation surgery followed by whole breast radiation therapy could be safely and effectively performed after neoadjuvant chemotherapy.[2,3] Nonetheless, this lack of evidence emphasizes the importance of comprehensive consensus regarding radiation therapy indications and radiation targets after NAC, including critical information, such as the presence or absence of pathologic response to the decision-making process.

Benefit of radiation therapy in breast cancer patients who received NAC is mainly based on retrospective studies. These series demonstrated a solid motivation for the use of PORT to the breast/chest wall and regional nodes for locally advanced breast cancer patient at presentation. In addition, in a subset of stage II disease with high-risk for loco-regional recurrence, the use of PORT was related to better clinical outcomes.[19–28]

In our Institution, patients treated with NAC followed by surgery, PORT is recommended based on initial clinical stage disease and recurrence risk factors. This is the reason why all included patients received irradiation treatment. As presented in Fig. 1, most of patients underwent mastectomy or nipple-sparing/skin-sparing mastectomy and received PORT for the chest wall, supraclavicular and axillary (levels II/III) regions with conventional dose. Factors that were related to the addition of regional lymph node irradiation were clinical tumor and nodal stage, pathological nodal stage, type of surgery and axillary dissection (Table 3).

The OS and DFS (Figs. 2 and 3) reported in this study were acceptable and comparable with other series.[19–22] There was no difference in loco-regional recurrence according to the type of surgery and there were statistically significantly fewer distant recurrences in the breast-conserving surgery group, suggesting that differences in PORT (Table 2) may have had an important role in both loco- and metastatic recurrence. However, due to the retrospective nature of the study, we cannot rule out potential bias, especially the risk of higher allocation of patients with more advanced disease to more radical surgery.

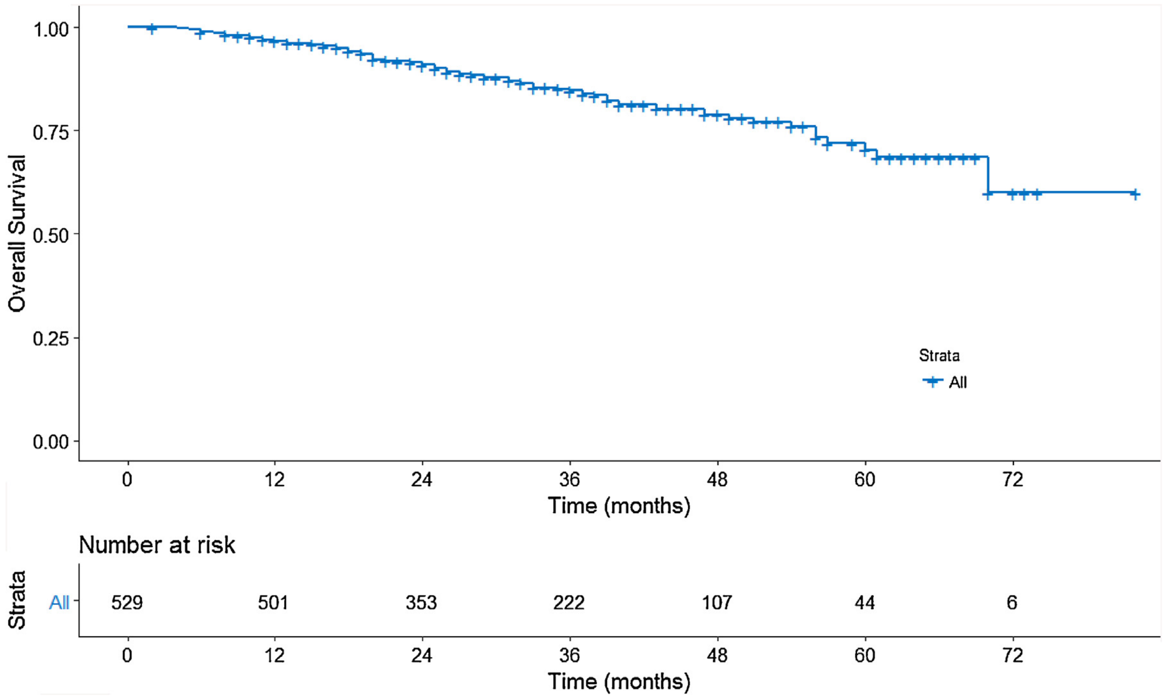

Fig. 2 – Overall survival.

In our study, there was no relationship between nodal irradiation fields and clinical outcomes (Supplemental table* 1 and Supplemental Figures) in an exploratory analysis. However, most of the patients received radiation therapy of the supraclavicular and axillary (levels II and III) nodes while level I axillary and internal mammary nodes were uncommonly employed. An adjusted analysis for confounders would be underpowered and, therefore, no firm conclusion can be drawn based on these findings.

Moreover, in our cohort, internal mammary radiation was used in only 9% of the patients, highlighting a hesitancy to accept targeting of this area as having an important role on disease outcomes. Although not specifically evaluated in the NAC setting, some studies have addressed this issue in the

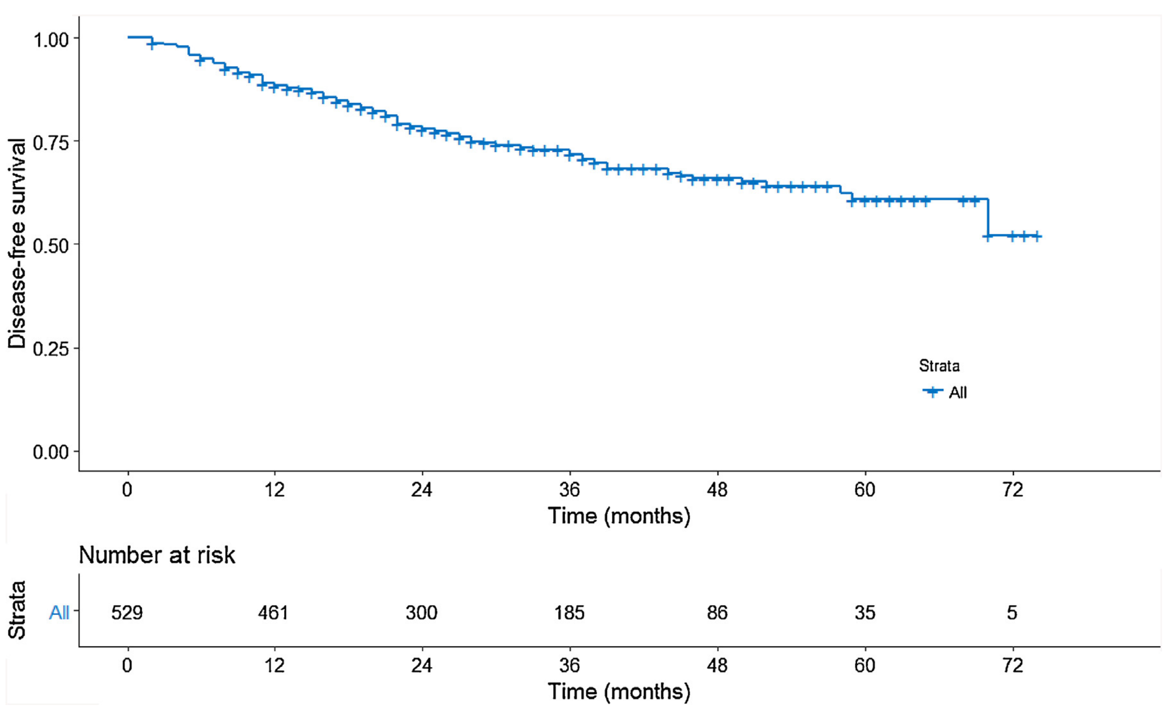

Fig. 3 – Disease-free survival.

adjuvant setting, with somewhat contradictory results – though usually supporting some level of benefit from the addition of internal mammary chain to regional nodal irradiation.[29–31] Because of the retrospective nature of our study and the low number of patients treated with internal mammary radiation, no insights on this issue can be drawn from our data.

Some authors suggested that in patients who had complete response (pCR) after NAC PORT could be omitted. It is indeed known that the magnitude of response to NAC is related to prognosis; better disease-free and overall survival rates are observed in those who had a complete pathologic response – though this appears restricted to the more biologically aggressive subtypes (triple negative, Her2 positive and, possibly, luminal B).[32] Of note, in our cohort, 44.4% of the patients had luminal subtypes profile, in which the validity of this concept is unclear. In summary, although this concept is appealing, the strategy of omitting PORT after pCR or near-pCR needs validation from prospective clinical trials.[14,15,26] There are two ongoing studies that might help address those unsolved issues. NSABP B-51/RTOG 1304 trial[33] is evaluating whether it is oncologically effective and safe to restrict the magnitude of radiation therapy in patients with breast cancer, clinical T stage 1–3, N1, and that become N0 after neoadjuvant chemotherapy. Similarly, Alliance A011202 trial[34] is assessing whether axillary radiation therapy is as effective as lymph node dissection in patients with node-positive breast cancer treated with neoadjuvant chemotherapy followed by surgery.

In conclusion, our study suggests that the use of PORT to breast/chest wall with or without regional nodal area is an effective strategy, associated with acceptable disease-free and overall survival rates in patients with fairly locally-advanced breast cancer treated with NAC followed by surgery. Until further evidence becomes available, initial disease stage and classical risk factors for recurrence should be routinely employed to guide PORT and radiation fields in this setting.

Conflict of interest

None declared.

Financial disclosure

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpor.2018.11.002.

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