

Locoregional Control After Breast Conserving Treatment in Patients Undergoing Neoadjuvant Chemotherapy for Breast Cancer

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Abstract

In the last decade Neoadjuvant Chemotherapy (NAC) has become more common for patients with operable breast cancer. Greatest advantage of this approach is that it can increase the proportion of patients who can be treated with Breast Conserving Therapy (BCT). This is a retrospective study of a prospective database regarding 573 patients, consecutively treated with BCT and ALND, among these 84 were treated with NAC. Primary end-point of this study was to evaluate long-term outcomes of patients treated with BCT after NAC. Secondly we evaluated same outcomes in populations with comparable initial clinical stage; moreover factors affecting the risk of developing a Locoregional Recurrence (LRR) were investigated. Incidence rate registered for LRR was 1/100 person per year for patients treated with adjuvant chemotherapy, while it is doubled in the NAC-group with 2/100 person per year. Ipsilateral breast tumour recurrences' incidence rate was 1 IBTR per 100 persons per year in the first group and twice as much in the NAC-group. When considering only patients initially staged cT2, there is no significant difference in terms of outcome at 5 and 10 years. NAC shows equivalent outcomes compared to BCT and adjuvant chemotherapy especially when our case-series is analyzed by presenting clinical tumor stage, leading to satisfactory locoregional outcomes without affecting overall survival of patients, thus increasing considerably the rates of patients eligible for conservative treatment.

Keywords: Breast Cancer; Conservative Treatment; Locoregional Recurrences; Neoadjuvant Chemotherapy

Introduction

Neoadjuvant Chemotherapy (NAC), initially used only for locally advanced and inflammatory breast cancer, has become more common also for patients with operable disease. Although there is no clear survival benefit for patients treated with NAC compared with adjuvant chemotherapy, greatest advantage of this approach is that it can increase the proportion of patients who can be treated with Breast Conserving Therapy (BCT); moreover it allows assessment of disease response to a specific medical treatment [1-3]. To date, there is limited information on rates and predictors of Locoregional Recurrence (LRR) and Ipsilateral Breast Tumor Recurrence (IBTR) for patients who undergo NAC. Other authors explained the paucity of data on this topic with two reasons, first considerably fewer patients with operable breast cancer are being treated with NAC versus adjuvant chemotherapy. Second, by the time NAC became established as an alternative to adjuvant chemotherapy, the role of locoregional External Radiotherapy

(xRT) in patients with positive lymph nodes was well established, therefore most of the data available on NAC, include patients treated, at physicians' discretion, with postoperative xRT (because of pathological findings of positive nodes or because nodes were presumed to be positive before commencement of NAC) [4]. A previous attempt to compare NAC and adjuvant chemotherapy, in terms of locoregional control was made by Mauri et al. in 2005, through a meta-analysis, which demonstrated equivalency between the two techniques in terms of survival and overall disease progression, but reported a significant increase in the risk of LRR in the NAC setting. As the author stated, a considerable number of patients included in the study did not undergo surgery after NAC, especially when an apparently complete clinical response was achieved and were treated only through xRT [5]; this practice is surely unadvisable and has negatively affected the outcomes.

An open issue in this specific setting is lack of standardization on surgical approach for patients treated with NAC who become eligible for BCT, which also contributes to uncertainty in determining factors affecting loco-regional control. Many authors declare to avoid any attempt of resecting the initial volume of the

disease [6-8]. In our institution, surgical approach for patients treated with NAC, is based on the “neoadjuvant net” technique, details and early outcomes, about this topic have been previously published [9] and it already proved to be practical, cost-sustainable, easy to reproduce and also effective on the short-term. The aim of this analysis is to compare a population of patients treated with BCT and Axillary Lymph Node Dissection (ALND) after NAC (NAC-group), with a consecutive case series of patients also treated with BCT and ALND, in the same time period, for which NAC was not indicated (postoperative chemotherapy group). Purpose of this comparison, even in the awareness of difference in the initial clinical stage, was to show that NAC can lead to outcomes comparable to those obtained in patients diagnosed with early breast cancer treated with surgery first, especially for subgroups of patients with equal clinical stage, emphasizing the role of NAC in increasing the proportion of patients who can be treated with Breast Conserving Therapy (BCT) and helping standardizing BCT after NAC.

Patients and Methods

This is a retrospective study of a prospective database regarding 573 patients, consecutively treated with BCT and ALND for breast cancer at Sant’ Orsola-Malpighi Breast Unit, between January 2000 and January 2014. Patients originally operated in other hospitals and treated in our institution only for occurrence of LRR (n = 12), those who underwent a mastectomy soon after first intervention for gross margins involvement (n = 4) and one patient who spontaneously decided to undergo a skin-sparing mastectomy in another institution due to recurrent mastitis few months after first intervention, were excluded. Cases lost to follow-up were 24. Among the remaining 532 cases, 84 were treated with NAC first, while the remaining 448 underwent surgery upfront and adjuvant chemotherapy, when indicated. None of the 84 NAC cases was eligible for breast conserving treatment at the time of diagnoses. Totally patients who underwent BCT after NAC in our institution in the same time period represent 53.1% of all patients treated with NAC, the rest of them was treated with total mastectomy. Primary end-point of this study was to evaluate long-term outcomes of patients treated with BCT after NAC. Measured outcomes were 5 and 10 years IBTR-free survival and LRR-free survival. Results obtained were compared to a population of patients treated with BCT and ALND in the same time period, for whom NAC was not indicated (PoCT-group). Secondarily we evaluated same outcomes in populations with comparable initial clinical stage. Purpose of this comparison, even in the awareness of difference of the initial clinical stage, was to show that NAC might lead to outcomes comparable to those obtained in patients diagnosed with early breast cancer treated with surgery first, emphasizing the role of NAC in increasing the proportion of patients who can be treated with Breast Conserving Therapy (BCT). 5 and 10-years Disease Free Survival (DFS) and Overall Survival (OS) were also calculated.

Finally, factors potentially affecting risk of developing LRRs were identified and investigated through multivariate analysis.

LRR was considered as recurrent disease in ipsilateral breast or lymph nodes of axilla, supraclavicular or infraclavicular fossae and internal mammary nodes. While IBTR was considered any recurrence occurring in the treated breast, regardless of the time passed since day of surgery. All tumors occurring in contra-lateral breast were registered as new primary. DFS was calculated from the date of surgery to the date of the diagnosis of the recurrence; OS from the date of surgery to death (both disease related or from other causes). Rate of pathologic complete response in the NAC-group was registered and its impact on IBTR rate was evaluated and reported. The following data were considered as possible factors for predicting the risk of recurrence: initial clinical nodal status (cN0 or cN+), initial clinical T-stage, surgical specimens’ margins involvement (positive or negative - positive margin was considered presence of neoplastic cells on the resection inked margin), istopathological lymph-nodal stage (pN0 vs pN1 vs pN2+), estrogenic receptor expression (ER<1% vs 1%≤ ER ≤10% vs ER>10%), Ki67 index (cutoff 20%), HER2 status (positive or negative) and of course administration of neoadjuvant chemotherapy.

Pathologists of our Center analyzed all postoperative specimens. In cases of patients treated with NAC, our pathologists always evaluated pre-treatment biopsy and immunoistochemical profile; when patients came from other institutions, specimens were reviewed in our Center. Initial tumor size in millimeters was not reported, since it was characterized by a vast heterogeneity in terms of evaluation methods (mammography, US, RM), therefore we considered more reliable initial clinical T-stage, which was always measured at the time of diagnosis and for patients undergoing NAC, reported on the “neoadjuvant net” by a surgeon of our team. In our institution, whole breast irradiation is obviously part of BCT, always in cases of invasive tumor; regarding management of axillary nodes positivity, radiotherapy was administrated only when four or more positive lymph nodes were identified on pathological definitive examination. Standard radiation dose for the breast is 50 Gy divided in 25-28 fractions of 1,8-2 Gy each, administered daily, for 5 days a week, for approximately 5 weeks; the same for axilla and supraclavicular fossa, when indicated. A boost of totally 10-16 Gy is administered to the surgical bed in the following cases: pT>2, positive surgical margins, pN2+ and patients younger than 45. Follow-up visits with physical examination were conducted every 6 months for the first five years and annually thereafter, until ten years from surgery. Once a year patient undergo mammography, breast ultrasonography and chest X-ray. For patients who did not develop any recurrence after ten years from surgery, reintroduction in the general population mammographic screening program was recommended and a yearly follow-up phone call was carried out.

According to the initial stage of the diagnosed breast cancer, follow-up program could be intensified, and more diagnostic tools might have been used on a regular base such as (total body CT-scan, PET-scan, bone scintigraphy) especially in cases of patients belonging to the NAC-group. Chemotherapy regimens over the time of the study period varied and details regarding the NAC regimens followed by the patients were not always present in our records and were not considered determinant for the main endpoints of our study, therefore were not reported. All survival curves were estimated using the Kaplan-Meier method. Cox regression stepwise analyses were used to identify factors affecting recurrence incidence in multivariate analyses. Two-tailed P values less than 0.05 were considered statistically significant. All statistical analyses were carried out through the Statistical Package for the Social Science (SPSS, Chicago, IL), version 13.

Results

Clinicopathological characteristics of the studied population are reported in (Table 1). A series of differences between these two

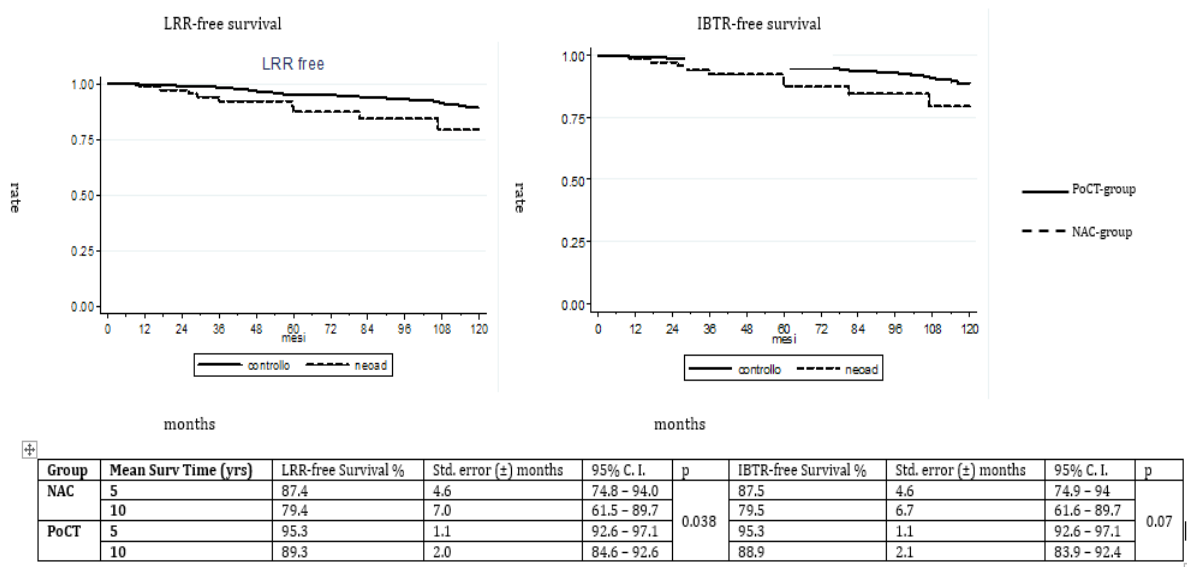
populations is remarkable, as far as initial clinical tumor stage, lymph-nodal pathological stage and Estrogen Receptors (ER) expression, but this was inevitable in order to avoid a selection bias. Patients who did not undergo NAC were, of course, patients with smaller tumors rather than non-palpable lesions. In contrast cT3 stages were mostly uncommon among these patients, since they represent one of principal indications to NAC. Totally, 32/448 (7.1%) cases of IBTR were registered among patients treated with BCT and adjuvant chemotherapy, while 9/84 (10.7%) cases were registered in the NAC-group. Median age in the NAC-group was 49 years (range, 32 - 83 years) while in the PoCT-group it was 59 years (range, 28 - 86 years). Mean follow-up time was 90 months (range 12 - 178) for the PoCT-group and 68 months for the NAC-group (range 12 - 181). LRR occurred in 37 (8.2%) patients in the PoCT-group and in 9 (10.7%) patients in the NAC group; if we exclude IBTRs, only 1 LRR occurred in the NAC-group (synchronous to the IBTR) and 12 in the PoCT-group. NP were 1 vs. 17 (1.2% vs. 3.8%), respectively.

	cT	n. (%)	cN	n. (%)	G	n. (%)	pN	n. (%)	Marg is	n. (%)	Marg inv	n. (%)	ER status	n. (%)	Ki67	n. (%)	HER2 status	n. (%)	Tot
NAC-group	cT1 (a-c)	6 (7.1)	cN0	33 (39.3)	1	17 (20.2)	0	40 (47.6)	Free	84 (100)	Free	78 (92.6)	0-0.9	27 (32.1)	<20	35 (41.7)	Neg	46 (54.8)	84
	cT2	51 (60.7)	cN1	45 (53.6)	2	27 (32.1)	1	28 (33.3)	Close	0	Close	0	1-10	1 (1.2)			1	1 (1.2)	
	cT3	25 (29.8)	cN2	6 (7.1)	3	20 (23.8)	2	16 (19.1)	Positive	0	Positive	6 (7.1)	>10	54 (64.3)	≥20	49 (58.3)	2	2 (2.3)	
	cT4	2 (2.4)			n.a.	20 (23.8)							n.a.	2 (2.4)			3	35 (7.8)	
PoCT-group	cT1 (a-c)	360 (80.3)	cN0	359 (80.1)	1	104 (23.2)	0	125 (27.9)	Free	419 (93.5)	Free	421 (94)	0-0.9	46 (10.2)	<20	229 (51.1)	Neg	220 (49.1)	448
	cT2	85 (19)	cN1	83 (18.5)	2	174 (38.8)	1	252 (56.3)	Close	29 (6.5)	Close	20 (4.5)	1-10	9 (2.1)			1	129 (28.8)	
	cT3	0	cN2	6 (1.3)	3	170 (38)	2	71 (15.9)	Positive	0	Positive	7 (1.6)	>10	387 (86.4)	≥20	219 (48.9)	2	49 (10.9)	
	cT4	3 (0.7)			n.a.	0							n.a.	6 (1.3)			3	50 (11.2)	

Table 1: cT=initial clinical stage, cN=initial lymph-nodal stage, G=grade, n.a.=not available. cT4 excluded T4d, pN= pathologic lymph-nodal stage, Marg is= presence of carcinoma in situ on surgical margins, Marg inv= presence of invasive carcinoma on surgical margins, free = ≥ 1 mm distance of tumor from margins, close = < 1 mm distance tumor from margins, positive = presence of ink on tumor foci, n.a.=not available.

5 years LRR-free survival for NAC group resulted 87.4% vs. 95.3% in PoCT-group; while 10 years LRR-free survival was respectively 79.4% and 89.3% (p = 0.038) (Figure 1); which converted in incidence rate means that in the PoCT-group LRR occurs in 1/100 person per year, while it is doubled in the NAC-

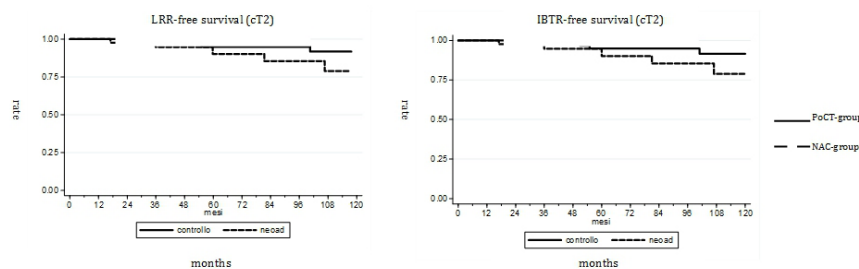
group with 2/100 person per year. 5 years IBTR-free survival for NAC group resulted 87.5% vs 95.3% in PoCT-group; while 10 years IBTR-free survival was respectively 79.5% and 88.9% (p = 0.07) (Figure 1).



Converted in incidence rate, we would register 1 IBTR per 100 persons per year, twice as much in the NAC-group with 2/100 person per year. The similarity between the results for LRR and IBTR occurrence is because in the whole studied population, only in 6 cases a LRR occurred independently from an IBTR (in 1 patient in the NAC-group and the remaining 5 belonging to the PoCT-group). In all other cases, LRRs occurred subsequently an IBTR, therefore they were not determinant for the LRR-free Kaplan-Meier curve; more over considered that all treated patients underwent ALND, incidence of lymph nodal recurrence was severely reduced.

Interestingly when considering only patients initially staged

cT2, yet recognizing the paucity of cases examined, there is no significant difference in terms of outcome at 5 and 10 years, for PoCT-group (n. 85) vs NAC (n. 51), 5 years LRR-free survival respectively 94.9% vs. 90.2% and 10 years LRR-free survival respectively 91,7% vs 78.9% - p = 0.14. In other words, in the PoCT-group the rate of LRR is 0.73/100 person per year, while in the NAC-group 1.84/100 person per year. While in terms of IBTR 5 years and 10 years IBTR free survivals were 90.2% vs. 94.9% and 78.9% vs 91.7%, p= 0.14. (Figure 2) DFS at 5 and 10 years for PoCT vs. NAC-group, as predictable was significantly different, respectively 88.9% vs. 77% 5 yrs DFS and 75.1% vs. 59.8% 10 yrs DFS (p<0.05).



While 5 years OS resulted 93% vs. 86.2% and 10 years OS 83% vs 83.5% (p=0.30) respectively. Another peculiar result of the analysis of our population is the relationship between pathological complete response (pCR) after NAC and tumor recurrences. Among the 84 cases treated with NAC, pCR was obtained in 16

cases (19%), in this subset of patients no recurrences occurred, whether LRR or IBTR. Results of multivariate analysis for LRR, showed that the only variable significantly affecting loco-regional control in the overall studied population is ER status, demonstrating a protective role against LRR (HR 0.66 - p=0.03), while even if it

does not reach the threshold of statistical significance, evidence of lymph nodal metastasis shows to increase the risk of developing a LRR (HR 1.51 - $p = 0.06$) (Table 2). Considering instead the impact of the same variables on IBTR occurrence, there was only one factor affecting the outcome and interestingly it was NAC (HR 3.71 - $p = 0.01$) (Table 3).

	HR	95% C.I.	P
cN	0.91	0.42 to 1.94	0.8
cT	0.64	0.37 to 1.09	0.1
Margins (neg. vs pos.)	2.67	0.79 to 9	0.16
pN	1.34	0.82 to 2.2	0.24
ER expression (< 1% vs ≤ 10% vs > 10%)	2.5	0.50 to 1.10	0.11
Ki67 (< 20% vs ≥ 20%)	1.16	0.57 to 2.4	0.17
HER2 status	0.89	0.65 to 1.16	0.34
NAC	3.71	1.36 to 10.09	0.01

Table 2: Multivariate analysis results for IBTR - cN=initial clinical lymph-nodal stage, cT=initial clinical tumor stage, pN=pathological lymph-nodal stage, NAC=treated with neoadjuvant chemotherapy.

	HR	95% C.I.	P
cN	1.07	0.54 to 2.01	0.85
cT	0.73	0.44 to 1.20	0.21
Margins (neg. vs. pos.)	1.87	0.54 to 6.54	0.33
pN (neg. vs. 1-3 pos vs. 4+)	1.51	0.98 to 2.34	0.06
ER expression (< 1% vs ≤ 10% vs > 10%)	0.66	0.46 to 0.96	0.03
Ki67 (< 20% vs ≥ 20%)	1.27	0.66 to 2.44	0.47
HER2 status	0.84	0.64 to 1.11	0.23
NAC	1.74	0.83 to 3.68	0.14

Table 3: Multivariate analysis results for LRR - cN=initial clinical lymph-nodal stage, cT=initial clinical tumor stage, pN=pathological lymph-nodal stage, NAC=treated with neoadjuvant chemotherapy.

Discussion

Even if there is not a clear significant difference between the two populations in terms of IBTR-free survival, we cannot state with certainty that in the NAC group we have comparable loco-regional outcomes at 5 and 10 years. The results indeed show a trend toward an increase of incidence of recurrences in the NAC group. This trend is confirmed and elucidated by the results of the multivariate analysis (Table 2), which shows us how undergoing

NAC, raises itself the risk of developing an IBTR (HR 3.76 - 95% C.I. 1.36 to 10.09; $p = 0.01$), this is logically due to the fact that in this cohort of patients, there is an automatic selection of cancers with higher stage and more aggressive biological features, therefore determining an increase in the rate of IBTR and LRR compared to patients who did not undergo NAC. Favorable outcomes identified in patients affected by tumors over-expressing estrogen receptors are in line with all the recent findings on this matter. Recent studies already demonstrated lower incidence of local recurrence for luminal A and B tumors [10] and as other authors confirmed, tumor biology plays a crucial role in determining local control, just as important as microscopic residual disease burden [11].

Results obtained among patients who obtained pCR correlate to previous published data, showing an improvement in the outcomes in terms of disease recurrence, for patients who experience pCR, which itself carries a potential increase of the rates of BCT after NAC [4,12,13]. The 87.5% reported 5 years IBTR-free survival in the NAC group, is in line with results previously published by other authors [2,14-16], even if there is an evident lack of randomized control trials on this topic, leaving actual knowledge and evidences to retrospective analysis, each one carrying its own limitations and that sometimes are based on case series that might result outdated [2]. We are aware of the average stage difference between the two populations examined and also that the number of patients, especially those treated with NAC, is limited. More over the observation period of the study of about fifteen years includes automatically a series of progresses and changes in the treatment protocols that might have affected survival and locoregional control in different ways, but the advantage of our study is that it is based on a single center, consecutive, case series of patients, treated through a well-established surgical method, allowing a better and clear understanding of factors affecting the outcomes. In agreement with a previously published case series, in which authors analyze the outcomes of patients treated with NAC and BCT vs. BCT and postoperative chemotherapy per presenting tumor stage, [17], results obtained in the cT2 subset, induce us to believe in the effectiveness and safety of NAC, leading to an increase of the number of patients who can benefit of BCT and showing equivalent outcomes obtained with BCT and adjuvant chemotherapy, thus representing a clear advantage for patients.

Concerning axillary lymph-nodes management, patients in the NAC-group always underwent ALND. The reason is that to our knowledge, in the time period examined there was no clear evidence yet that Sentinel Lymph Node Biopsy (SLNB) could be a reliable technique in this set of patients. Few studies in the recent years have tried to address this question; first attempt to clarify role of SLNB in patients undergoing NAC for operable cancers was a meta-analysis published in 2006 in which authors evaluated sensitivity and identification rate of SLNB in this specific setting and it resulted to be a reliable tool for planning treatment after

preoperative chemotherapy and an accurate technique for determining the need for ALND in patients clinically node-negative following preoperative chemotherapy [18]. More recently other three studies were published, pushing beyond the understanding of this topic and evaluating patients with known node positive breast cancer prior to NAC. The first two are ACOSOG Z1071 trial and SENTINA study, in both cases feasibility of SLNB following NAC remained uncertain [19,20]. This is mainly due to low detection rates registered and raised false negative rates, especially when only one SLN is harvested, leading to an increase of undetected residual axillary disease, which in the NAC setting, differently from the adjuvant setting, might determine an increase of the risk of recurrence. The latest study is the SN-FNAC, in which the SLN identification rate resulted 88% and FNR only 8.4; interestingly, if sentinel nodes with isolated tumor cells were not included as “positive” sentinel node, the FNR was higher (13.3%) [21]; this trial closed early due to low accrual, only 153 patients of the 300 planned. Main question in this field remains: can residual tumor be left behind after NAC without altering the prognosis? [12].

Considering patients treated with BCT and adjuvant chemotherapy, ALND was performed for all patients with clinical suspicion of axillary lymph node metastasis or tumors larger than 3 cm in diameter until 2005, following Philadelphia guidelines [22]; since 2005, ALND was performed only in cases of positive sentinel lymph node biopsy or preoperative cytological/histologic evidence of metastasis, in agreement with ASCO guidelines [23].

Conclusions

NAC can lead to an increase of patients who can benefit from BCT and shows equivalent outcomes obtained with BCT and adjuvant chemotherapy when our case-series is analyzed by presenting clinical tumor stage, representing a clear advantage for patients in terms of assessment of disease response to a specific medical treatment and of increase of the quote of patients who might benefit of BCT. NAC, nowadays, is principally adopted for patients presenting with high stage tumors and often with more aggressive bio-pathological features. As proven by our multivariate analysis, belonging to this set of patients carries an intrinsic higher risk (HR 3.76) of developing a local recurrence, therefore determining an increase in the rate of IBTR compared to patients who do not need NAC. On the other hand, application of proper regimens of NAC associated to a thorough surgical technique may significantly reduce this risk and lead to satisfactory locoregional outcomes without affecting overall survival of patients, thus increasing considerably the rates of patients eligible for conservative treatment.

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