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# Primary systemic therapy and whole breast irradiation for locally advanced breast cancer: A systematic review

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## Abstract

The current management of locally advanced breast cancer (LABC) is based on tri-modality treatment including chemotherapy, radiotherapy and surgery. The concept of preoperative concurrent or sequential chemoradiation for LABC was initially reported more than a decade ago; however this concept did not gain popularity because of the low benefit/risk ratio and the lack of strong data supporting the concept. The

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purpose of the current systematic review was to explore the published data about preoperative chemoradiation (sequential and/or concurrent) using whole breast irradiation in terms of toxicity and outcome.

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**Keywords:** Breast cancer; Chemoradiation; Chemotherapy; Irradiation; Neoadjuvant; Preoperative; Radiotherapy

## 1. Introduction

The current management of locally advanced breast cancer (LABC) is based on tri-modality treatment including chemotherapy, radiotherapy and surgery. The concept of concurrent or sequential chemoradiation for LABC was evaluated in the neoadjuvant setting using various chemotherapy regimens and several radiotherapy techniques (external beam, brachytherapy) and dose-fractionation schedules. Initial reports of neoadjuvant chemoradiotherapy (CT-RT) were published more than a decade ago [1–4]; however, this concept did not gain popularity because of the low benefit/risk ratio and the lack of strong data supporting its routine use.

The aim of neoadjuvant treatment for breast cancer is to downsize the tumor in order to preserve the breast with clear pathological margins and potentially to achieve pathological complete response (pCR) that could impact outcome in some subgroups of patients. Studies of neoadjuvant CT-RT for LABC can be subdivided according to whether the treatments (chemotherapy and radiotherapy) were given concomitantly or sequentially prior to surgery and whether radiotherapy was given to the whole breast or to the tumor only (partial breast irradiation). The surgical approach also differs between the studies; some aimed to increase the rates of breast conservation while others included inoperable patients or patients who were planned to undergo mastectomy.

The purpose of the current systematic review was to explore the published data about preoperative CT-RT (sequential and/or concurrent) applying whole breast irradiation for LABC, to better understand why this concept did not gain popularity and to assess if there is a place to re-evaluate this treatment in the era of molecular understanding of breast cancer.

## 2. Methods

With the assistance of two medical librarians at our institution, an Ovid Medline search was performed, initially by using “neoadjuvant therapy” and “breast neoplasms”, both as major topics. Thereafter, both the subheadings were searched with “radiotherapy” or “irradiation” as major MeSH terms. Next, “radiotherapy” was combined with the MeSH term “breast neoplasms”. The search was limited to the past 10 years and to the English language, and resulted in 227 articles that were first evaluated by title and then by abstract. SciFinder was used as the second database. EMBASE search was not conducted due to limited access.

Full text articles were retrieved and reviewed for the selected titles and abstracts. Reference lists of the retrieved articles were searched for additional publications. The final reference list was generated on the basis of relevance to the subject of the review. Only studies of preoperative chemotherapy and external whole breast radiotherapy (conventional doses) were included. We included only data from published articles and not from abstracts presented at scientific meetings; we did not include preoperative brachytherapy and or preoperative low-dose external radiotherapy or preoperative radiotherapy alone. The results of the search did not enable us to perform a high quality meta-analysis due to the heterogeneity of the trials, and a major flaw of the published data in our view is that there are numerous publications coming from a limited number of institutions.

## 3. Combined chemoradiotherapy schedules in the neoadjuvant setting

### 3.1. Neoadjuvant concurrent chemoradiotherapy

The largest report of neoadjuvant CT-RT, which summarized several decades of experience, came from South India. Shanta et al. [1] reported a large retrospective series of 1117 consecutive cases of LABC treated by neoadjuvant CT-RT (concomitant CMF or ECF or ACF). The pCR rate, which was among the highest reported in the literature for neoadjuvant CT-RT, was 45.1%. pCR rates were correlated to the T stage; those with T2 (T1 not included) had a higher rate of pCR as compared to T4 with 35.6%. The best survival rate was seen among those who had pCR at the primary site and the axilla (tumor and node negative postoperatively). Interestingly, in patients who achieved pN0, the risk of disease recurrence and death was reduced by half compared to patients with pN1, irrespective of tumor complete response [1].

Skinner et al. [2] evaluated the use of continuous 5-fluorouracil (5-FU) with radiotherapy in inoperable non-inflammatory LABC in a prospective single arm study. 5-FU was given at a dose of 200 mg/m<sup>2</sup> as a continuous infusion for 8 weeks; radiotherapy to the whole breast and axilla was started on day 15 of chemotherapy and delivered a total dose of 50 Gy. Patients who were found operable after completion of neoadjuvant therapy underwent a mastectomy and adjuvant polychemotherapy. Ten of 36 patients required interruption in 5-FU treatment and nine patients suffered from in-field wet desquamation. Prior to neoadjuvant treatment, all patients were considered unresectable due to skin

involvement; after neoadjuvant treatment, all were eligible to undergo mastectomy. Seventeen percent had pCR at the time of surgery.

Using paclitaxel concomitantly with radiotherapy in the neoadjuvant setting, Skinner et al. [3] reported higher pCR rates (26%), but the patients included in this study had less extensive disease. As noted in Shanta's report [1], the pCR rates may be influenced by the T stage. Postoperative complications were more common in the paclitaxel regimen [1] (Table 1).

Preoperative concomitant paclitaxel and radiation in LABC was also investigated by Formenti et al. [4]. This group of investigators published numerous articles, both clinical and pre-clinical studies, on this topic as part of a multicenter study. The initial treatment regimen consisted of 60 mg/m<sup>2</sup> of weekly paclitaxel combined to whole breast radiation therapy delivering 50 Gy in 25 fractions over five weeks. However, the study protocol was amended due to severe skin toxicity in two patients. Paclitaxel dose was reduced to 30 mg/m<sup>2</sup> given twice weekly and the radiation dose/fraction also was reduced to fractions of 1.8 Gy for a total dose of 45 Gy over five weeks. The study aimed to evaluate the response rate in patients who were planned to undergo modified radical mastectomy followed by adjuvant doxorubicin-based chemotherapy. Surgery was performed at least two weeks after chemoradiation completion or after complete skin toxicity recovery.

Another report was published a decade later by Adams et al. [5]. The authors showed that a single paclitaxel agent given concomitantly with radiotherapy to the whole breast and nodal region could achieve pCR rates comparable to neoadjuvant polychemotherapy. However, in spite of the long median follow-up of 60 months, acute and late skin toxicities were not reported in this study. Unfortunately, the risk of skin toxicity and interstitial pneumonitis is known to occur with concomitant taxanes-radiotherapy [14]. Furthermore, as in other neoadjuvant CT-RT trials, all the patients received post-operative polychemotherapy (mainly doxorubicin based). Thus, the pre-operative strategy did not spare patients from receiving systemic post-operative polychemotherapy. In an attempt to find biological predictive markers for neoadjuvant treatment response, sequential biopsies were taken from the primary breast tumor during the neoadjuvant paclitaxel administration prior to concomitant chemoradiation. The investigators encountered difficulties in achieving biopsies from patients which resulted in evaluating only part of the planned analysis [6]. However, an association between pCR and MAP2 (microtubule-associated protein)-over-expression was found. This was related to the response to paclitaxel [7]. All studies of concomitant neoadjuvant CT-RT are summarized in Table 1 [1–13].

### 3.2. Neoadjuvant sequential chemoradiotherapy

Sequential RT-CT protocols can allow patient selection regarding tumor chemoresistance before combined therapy. For example, Colleoni et al. [15] evaluated the

response rate of chemoradiotherapy to explore the best option for primary treatment of breast cancer with chemoradiation alone for “good responders”. In their study, all the patients received neoadjuvant treatment with doxorubicin and cyclophosphamide (AC). Patients who were defined as “good responders” after three cycles of chemotherapy were treated with three additional cycles followed by whole breast external beam radiotherapy before surgery. Unfortunately this study did not show an additional effect of combined CT-RT after the first three cycles of preoperative chemotherapy. The pCR rate in this study was very low, 8%. Mild or moderate side-effects, including mucositis, nausea/vomiting and leucopenia, were reported without any toxic deaths or grades III–IV toxicities.

Two retrospective studies published by a German group [16,17] compared the use of neoadjuvant chemotherapy plus external beam whole breast radiotherapy versus the same neoadjuvant chemotherapy alone. The chemotherapy protocol consisted of four cycles of epirubicin and cyclophosphamide (EC). In cases of large tumors, three cycles of CMF were added. All chemotherapy cycles were given at three-week intervals. Whole breast radiotherapy delivered 50 Gy in 25 fractions and all patients received an electron boost to the primary tumor. Preoperative radiotherapy was preferred for patients with large tumors who were planned for surgery that included a flap-support, to avoid postoperative irradiation. Anti-estrogen treatment was given after chemotherapy for patients with estrogen receptor (ER) positive tumors. The CT-RT group achieved significantly higher pCR rates (3% versus 42%). A logistic regression analysis indicated that hormone receptor status and neoadjuvant radiotherapy were statistically significant for pCR prediction. These two parameters were also independent prognostic factors in a multivariate analysis. Interestingly, the group of patients that had ER positive tumors and were treated by anti-hormonal agonists (GnRH agonist or tamoxifen) had a higher rate of pCR. In terms of toxicity, the authors stated that the side effects were mild to moderate in the CT-RT group.

These results are not supported by the results of other trials that evaluated response to neoadjuvant treatment. The authors suggested that the higher rate of pCR in the CT-RT group might be a result of the time interval between treatments, as the CT-RT group had a significantly longer time interval. This observation was also reported in other CT-RT trials and is addressed later in this text. As opposed to these results, Colleoni's study [15] did not show that the addition of neoadjuvant radiotherapy significantly increased the rate of pCR. It is impossible to compare these studies as the patient populations are different and there is not much information with regard to molecular subtypes. What is evident from these studies is that in Colleoni's study [15], the group of patients who responded well to neoadjuvant chemotherapy received additional pre-operative radiotherapy, whereas in the study by the German group [16,17] patients with more advanced T-stage, who were planned for more extensive surgery, were treated with CT-RT. These studies did not relate to long-term follow-up or survival. All studies are summarized in Table 2.

Table 1  
Trials of neoadjuvant concomitant chemoradiation.

Author (year) [Ref.]	No.	Total dose (dose per fx)	Chemotherapy protocol	Skin complications	Response
Semiglazov <sup>b</sup> (1994) [8]	137		<i>Concomitant</i> TMF <i>Adjuvant</i> (after surgery) TMF		pCR 29.1%
Skinner (1997) [2]	30	50 Gy (2 Gy)	<i>Concomitant</i> 5-FU	30% wet desquamation	All patients considered unresectable due to skin involvement; all underwent mastectomy; 20% had minimal microscopic disease, pCR 17%
Skinner (2000) [3]	29	45 Gy (1.8 Gy)	<i>Concomitant</i> Paclitaxel <i>Adjuvant</i> (after surgery) Doxorubicin-based chemotherapy	Minimal at time of radiation Two patients suffered from recall dermatitis at time of adjuvant	pCR 26% Two had partial pathological response
Formenti <sup>c</sup> (1999, 2003) [1,9]	44	45 Gy (1.8 Gy) 14 Gy boost	<i>Concomitant</i> Paclitaxel <i>Adjuvant</i> (after surgery) Doxorubicin-based chemotherapy	Grade 3 (7%) (2 cases were seen at the higher paclitaxel dose)	Clinical response rate 91% pCR 16%
Chakravarthy <sup>c</sup> (2006) [6]	30	46.8 Gy (1.8 Gy)	<i>Prior to RT</i> Paclitaxel <i>Concomitant</i> Paclitaxel <i>Adjuvant</i> (after surgery) AC	Grade 3 (one patient) Grade 4 (one patient)	Difficult to conclude from study response of group that received the concomitant treatment (30/38) pCR reported for whole group 34%
Bollet (2006, 2011) [10,11]	60	50 Gy (2 Gy)	<i>Prior to RT</i> 5-FU and vinorelbine <i>Concomitant</i> 5-FU and vinorelbine		pCR 27%
Shanta <sup>a</sup> (2008) [1]	1117	40 Gy (2 Gy) Some received also postop RT to internal mammary	<i>Concomitant</i> CMF (85%) ECF FAC	Mostly deep pigmentation Mild–severe dry epidermis Occasionally moist desquamation	pCR 45.1%
Alvarado-Miranda <sup>a</sup> (2009) [12]	112	50 Gy (2 Gy) 10 Gy electron boost to palpable residual disease	<i>Prior to RT</i> FAC AC <i>Concomitant</i> MTCF GC Both included dexamethasone (16 mg) <i>Adjuvant</i> FAC AC Paclitaxel	NR	pCR primary tumor 42% pCR (primary and nodal) 29.5%

Table 1 (Continued)

Author (year) [Ref.]	No.	Total dose (dose per fx)	Chemotherapy protocol	Skin complications	Response
Adams <sup>c</sup> (2010) [5]	105	45 Gy (1.8 Gy) 14-Gy boost	Prior to RT Paclitaxel (36 patients) Concomitant Paclitaxel ± trastuzumab (8 patients, from 2006) Adjuvant (after surgery) Doxorubicin-based chemotherapy	NR	pCR 34%
Matuschek <sup>a</sup> (2012) [13]	315	50 Gy (2 Gy) 10-Gy Brachytherapy boost (101 patients) With hyperthermia or 10 Gy electron boost	Concomitant (113 patients) EC CMF Mitoxantrone AC	NR	Primary tumor pCR 36.8% (includes both sequential and concomitant treatment) Nodal pCR: 68.9% (49.5% were cN0) pCR (primary tumor and nodal): 29.2%

Notes: 5-FU, 5-fluorouracil; TMF, thiotepa, methotrexate and 5-FU; AC, doxorubicin, cyclophosphamide; EC, epirubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-FU; ECF, epirubicin, cyclophosphamide, 5-FU; FAC, 5-FU, doxorubicin, cyclophosphamide; MTCE, mitomycin C, 5-FU; GC, cisplatin, gemcitabine; pCR, pathological complete response; pPR, pathological partial response; NR, not reported.

<sup>a</sup> Retrospective study.

<sup>b</sup> The study compared preoperative CT-RT versus radiotherapy alone prior to mastectomy.

<sup>c</sup> Multicenter study, Formenti et al.

#### 4. Locoregional results of neoadjuvant chemoradiotherapy

##### 4.1. Pathological complete response

In the context of neoadjuvant strategy, the potential impact of survival remains a key point for some subgroups of patients with triple negative and HER2+ tumors. Previous neoadjuvant trials have demonstrated that there is great difference in pCR rates with regards to tumor subtype and chemotherapy regimen. Great attention should be given to reported pCR rates, as the definition of pCR differs between trials considering (or not) primary tumor and nodal response. Some authors define pCR in the primary tumor only with/without the in situ component, while others include nodal negative status or residual tumor mass of less than 5% without mitoses [4,5,9,13,15,20,21]. It is obvious that the definition itself can greatly influence the rate of pCR. Some authors reported the rate of “pathological response” including both complete and partial pathology response. The definition of “partial response” also varies between studies; some defined it as less than 10 microscopic foci of viable invasive tumor while others defined partial pathological response as a reduction in the diameter of the tumor of more than 50% (WHO definition for partial response) [5,13]. This is confusing since macroscopic evaluation of the primary tumor after surgery will probably differ from the clinical estimation of the tumor prior to therapy, and it also depends on the means used to clinically evaluate the tumor size (palpation only, type of imaging). The lack of concordance between clinical and pathologic response is supported by numerous trials [2,9]. Formenti et al. [9] reported that only two patients with a clinical complete response had pCR and five among 35 patients with a clinical partial response were found to have a pCR.

Adams et al. [5] indicated that disease-free survival and overall survival were similar for patients who had pCR compared to partial response, thus incorporated both in the “pathological response” group. Skinner et al. [2] indicated that, at the time of publication (median follow-up of 22 months), none of the patients who had pCR had recurrent disease.

In summary, the overall rates of pCR reported in the CT-RT neoadjuvant trials varied between 8% and 45% (Tables 1 and 2). This range is similar to that of neoadjuvant chemotherapy alone (with the exception of HER2 positive tumors treated by anti-HER2 containing regimens) [15,20,21]. Additionally, in most studies, the in situ component was not included in the pCR definition, as in situ disease was found to be relatively resistant to neoadjuvant treatment [2].

##### 4.2. Nodal down staging

Most studies included a nodal radiation field in the neoadjuvant setting (with/without internal mammary nodes) [4,5,15]. According to the retrospective series, nodal down

Table 2  
Trials of neoadjuvant sequential chemoradiation.

Author (year) [Ref.]	No.	Total dose (dose per fx)	Chemotherapy protocol	Skin complications	Response
Touboul (1996) [18]	97	45 Gy (1.8 Gy)	<i>Sequential</i> Doxorubicin, vincristine, cyclophosphamide, 5-FU Fifth course was given after radiotherapy <i>Adjuvant</i> (after surgery) Sixth course of chemotherapy after completion of local treatment Maintenance adjuvant chemotherapy regimen without anthracycline was prescribed (12 monthly cycles)	NR	Clinical complete response 34%
Colleoni (1999) [15]	23	50 Gy (2 Gy) 10 Gy boost	<i>Sequential</i> AC	Mild to moderate	pCR 8%
Aryus <sup>b</sup> (2000) [17]	55	50 Gy (2 Gy) 6–11 Gy Electron boost to tumor	<i>Sequential</i> EC For large tumors CMF was added <sup>a</sup> Other	Mild to moderate	61% breast conservation surgery
Gerlach <sup>b</sup> (2003) [16] (follow-up study)		50 Gy (2 Gy) Electron boost to tumor	<i>Sequential</i> EC For large tumors CMF was added <sup>a</sup> Other	Mild to moderate	pCR 42% pPR 51%
Lerouge (2004) [19]	120	45 Gy (1.8 Gy) Adjuvant boost in selective cases	<i>Sequential</i> Anthracycline-containing combinations <i>Adjuvant</i> Sixth course of anthracycline-containing combinations Maintenance adjuvant CT regimen without anthracycline		pCR 19% (primary site)
Matuschek <sup>b</sup> (2012) [13]	315	50 Gy (2 Gy) 10 Gy brachytherapy boost (101 patients) With hyperthermia or 10 Gy electron boost	Sequential (192 patients) EC CMF Mitoxantrone AC		Primary tumor pCR 36.8% (includes both sequential and concomitant treatment) Nodal pCR: 68.9% (49.5% were cN0) pCR (primary tumor and nodal): 29.2%

Notes: 5-FU, 5-fluorouracil; TMF, thiotepa, methotrexate and 5-FU; AC, doxorubicin, cyclophosphamide; EC, epirubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-FU; ECF, epirubicin, cyclophosphamide, 5-FU; FAC, 5-FU, doxorubicin, cyclophosphamide; MTCF, mitomycin C, 5-FU; GC, cisplatin, gemcitabine; pCR, pathological complete response; pPR, pathological partial response; NR, not reported.

<sup>a</sup> Some patients received other chemotherapy which was not stated in the text.

<sup>b</sup> Retrospective study.

staging could be translated into better survival [1]. In addition, patients who achieved pN0 had significantly better survival, irrespective of primary tumor pCR [1,19]. In the Shanta et al. study [1], 93% of the patients presented with clinically evident nodal disease; of those, 57.5% had pCR in the axilla. There was a statistically significant difference in the rates of pN0 in favor of the CMF group as compared to the anthracycline-based chemotherapy group (59% versus 46%,  $p < 0.004$ ).

Significant nodal down staging was also reported by Skinner et al. [2], when the irradiation field included the axillary nodes. However, the axilla should be treated using a standard technique because of the inability to ensure complete coverage of the axilla using only tangential fields [22].

In the German studies [16,17], irradiation fields did not include axillary lymphatic drainage. The authors claimed that all patients who had clinically positive lymph nodes responded clinically to the neoadjuvant chemotherapy and all underwent level I/II axillary dissection at the time of surgery. In their series, nodal post-operative irradiation was given more frequently to the supraclavicular fossa as compared to IMC, which was delivered to only three patients with central/inner tumors.

#### 4.3. Neoadjuvant chemoradiotherapy before salvage surgery

CT-RT has been evaluated in small series as a treatment option for patients with LABC who remained inoperable or became inoperable during conventional primary systemic therapy. In a first series of 14 patients, concurrent CT-RT was given as part of a rescue protocol, after progression during neoadjuvant polychemotherapy (vinorelbine, 5-FU based) in inoperable patients [23]. Locoregional radiotherapy delivered 50 Gy in 25 fractions to the whole breast and nodal areas. Ten patients received an additional “boost” to the primary tumor. All patients completed CT-RT sequence without chemotherapy dose reduction. Half the patients suffered from moist desquamation (grade 2) and half had dry desquamation (grade 1) skin toxicity. Out of 14 patients, two had complete clinical response, and 10 were rendered operable after combined treatment. Surgery was performed 4–8 weeks after radiotherapy. pCR and microscopic residual tumor were found in five patients. No significant postoperative complications were noted. This study emphasizes that there might be a role for concurrent CT-RT for response enhancement [23]. In another study, which included 28 patients who did not respond to neoadjuvant anthracyclines, capecitabine combined with radiation was given as salvage therapy [24]. After treatment, 23 patients became operable. One patient achieved complete response and three patients achieved near-complete response. Forty-six percent of the patients suffered acute skin toxicity (grades 1–2). No major toxicity was noted during treatment. Only one patient suffered from postoperative wound complication. Attention should be given to the fact that, in this study, the initial neoadjuvant protocol was

anthracycline based and the patients were not given taxanes subsequently, which was shown to increase response in this setting [21].

#### 4.4. Impact of tumor biology on response to neoadjuvant chemoradiotherapy

##### 4.4.1. Hormone receptors and proliferation

Patients who were found to have estrogen receptor (ER) positive tumors received anti-hormonal treatment (ET) [4,5,9,13]. Alvarado-Miranda et al. [12] considered the impact of ER expression on pCR after neoadjuvant treatment. In their series, 48% of the patients received ET. The univariate and multivariate analyses indicated that ER negative tumors were significantly more likely to show pCR after neoadjuvant CT-RT compared to ER positive tumors [12]. This was the only independent factor for a higher pCR. The other clinico-pathological factors (such as age, T stage, N-stage, histological grade) did not impact pCR. These findings are similar to the results reported by Adams et al. [5]. They reported pCR rates of 54% in ER negative versus 18% in ER positive tumors ( $p < 0.0001$ ). These results are similar to other findings using combined therapy [10,15,25] or neoadjuvant chemotherapy alone [20,21,26]. However, overall survival depends more likely on pCR than ER status. In the Adams et al. report, patients with hormone receptor (HR) negative tumors who achieved pathological response had a comparable overall survival to patients with HR positive tumors who achieved pathological response [5]. Conversely, Matuschek et al. [13] reported that patients with HR positive tumor had better overall survival, but this factor was not found to be associated with pCR.

High HR expression, low grade and poor proliferation as tested using Ki67 are known to be associated with better prognosis. There is a lack of data on the impact of these factors altogether on pCR after RT-CT. Colleoni et al. [15] is the only report that found a significant correlation between high Ki67 expression and response to preoperative CT-RT.

##### 4.4.2. HER2 status

There is lack of strong data on the impact of HER2 overexpression and molecular subtypes on pCR after RT-CT. The Adams et al. [5] trial was the only one that evaluated the correlation of pCR according to breast cancer subtypes. These data were only available for 85 patients (of 105 patients) and trastuzumab was only administered after its approval by the FDA in 2006, thus only eight patients were treated with trastuzumab in the neoadjuvant setting. Pathological response (complete and partial) is summarized in Table 3 according to different tumor subtypes, showing that HR negative tumors had better response to neoadjuvant treatment.

An early report by Formenti et al. [25], prior to the introduction of trastuzumab, found that low HER2 gene amplification was associated with a higher rate of pathological response to neoadjuvant CT-RT. The same was for ER negative tumors. Other potential biological markers of

Table 3

Pathological (partial or complete) response to neoadjuvant chemoradiation by Adams et al. [5].

HR-/HER2+	HR+/HER2-	HR+/HER2+	HR-/HER2-
7/14 (50%) <sup>a</sup>	6/34 (17.6%)	3/13 (23.1%)	13/24 (54.2%)
3/7 <sup>b</sup>			

<sup>a</sup> All patients including those not treated with trastuzumab.

<sup>b</sup> Trastuzumab-treated only (in the text the authors stated that eight patients received trastuzumab, although the results are for seven patients only).

response (such as apoptosis markers, tubulin, etc.) were not associated with pathological response [25].

## 5. Recurrence and survival after neoadjuvant chemoradiotherapy

The efficacy of primary treatment aims to reduce distance metastasis dissemination and would increase the probability of better survival. In a prospective single arm trial, Adams et al. [5] evaluated the 5-year results of 105 patients treated by neoadjuvant paclitaxel concurrent with twice weekly radiation. The authors pointed out that recurrence was mainly manifested by distant metastases and was observed in 29/105 patients. Of these, six were patients who responded (pCR and partial response) compared to 23 patients who were defined as non-responders after the initial neoadjuvant treatment. Pathologic response (complete and partial) was associated with improved long-term outcome, regardless of ER status. After a median follow-up of 60 months, the median disease-free survival and overall survival was not reached at the time the article was written. The median disease-free survival time of non-responders was 57 months, with a median overall survival time of 84 months. Matuschek et al. [13] reported that pCR was associated with long-term survival, while two more factors were found to be associated with better overall survival, pT0 and neoadjuvant treatment consisting of concomitant CT-RT.

## 6. Acute and late toxicity of neoadjuvant radiochemotherapy

### 6.1. Impact of the type of chemotherapy schedule

Toxicity of standard fractionated RT-CT depends of the type of CT and the irradiated volumes. In the trial reported by Shanta et al. [1], which included 1117 patients who were treated by different concomitant CT-RT schedules, RT interruptions rate in the CT-RT protocol was low. Some of the patients were treated with a chemotherapy regimen that included doxorubicin, well known to cause radiation recall dermatitis [27]. In that study, significant skin morbidity “occasionally occurred”, more seen in large pendulous breasts, implying that this skin toxicity was more associated with dose distribution rather than with the chemotherapy used. However, the authors indicated that the preferred

regimen was CMF given in most cases, and this was less toxic when combined with radiation. Systemic complications that caused RT breaks were neutropenia and/or vomiting that lasted 1–2 days and occurred in less than 5% of patients [1].

Despite the fact that skin toxicity during neoadjuvant treatment was considered limited and delayed surgery for five weeks following neoadjuvant CT-RT, up to 50% of patients had postoperative complications [3,6], mostly reported in patients who underwent mastectomy with/without reconstruction. Skinner et al. [2,3] published two studies, one with concomitant 5-FU and the other with concomitant paclitaxel, and indicated that concomitant 5-FU resulted in significantly less postoperative complications and good response to treatment.

Toxicity encountered at the time of concomitant chemoradiation (mitomycin C and 5-FU or cisplatin and gemcitabine) given after an anthracycline containing regimen, included grade 1–2 neutropenia (32.2%), grade 1–2 anemia (5.2%), and grade 3 radioepithelities in 22.4% of patients [12]. The concomitant treatment was given with 16 mg of dexamethasone that served both as an antiemetic and as a means to reduce the risk of radiation pneumonitis [12]. The authors indicated that none of the patients suffered from severe lung or cardiac toxicity at a median follow-up of 43 months (range, 7–125 months). Pneumonitis was not reported in any of the studies. Formenti et al. [9] reported one case of dyspnea during chemoradiation.

Skinner et al. [3] reported that two patients (who deviated from the protocol and underwent breast-conserving surgery) developed chronic radiation mastitis that persisted throughout the course of their postoperative chemotherapy which included doxorubicin.

### 6.2. Impact of the time to surgery

Chakravarthy et al. [6] planned a definitive surgery 3–4 weeks after completion of radiation; however, the protocol was modified to allow a 5–7 week interval after the last dose of radiation, as an increased rate of postoperative complications was noted in the first 12 patients. In 6/44 patients (13%), the time from beginning of chemoradiation to surgery was longer than three months due to skin toxicity. In this trial, the time to surgery was strongly associated with the degree of pCR. It was emphasized by the investigators that, despite cautious delaying of surgery until skin recovery was achieved, a significant rate of surgical complications was detected, which was related to persistent normal tissue morbidity from paclitaxel-based chemoradiation.

In the German studies [16,17], the time interval from the end of neoadjuvant treatment to surgery was significantly longer in the CT-RT group compared to the neoadjuvant chemotherapy group. This was due to acute effects of radiotherapy; however, wound complications were not increased in patients in whom the acute effects subsided prior to surgery. Patuschek et al. [13] also found that a long interval from completion of neoadjuvant treatment to surgery



was associated with an increased probability of pCR ( $p < 0.01$ ). Post-mastectomy complications occurred in 14% of the cases and included four infections with delayed wound healing, one tram flap necrosis that required revision, and one mastitis with grade 3 dermal injury [9].

In Colleoni's study [15], most patients underwent breast conserving surgery (70%), yet overall postoperative complications were frequent and included grade 2–3 infections that required prolonged antibiotic therapy and, in four cases, wound dehiscence was observed. The authors ascribed these postoperative complications to radiotherapy given prior to surgery.

Others suggested that optimizing the time to surgery, after recovery from radiation dermatitis (according to this study, 4 weeks), results in relatively good pCR rates and low complications rates [1,17]. The rates of seroma were greater than usual, seen in about 15% of cases. However, no major postoperative skin morbidity, such as skin necrosis or breakdown of incisions, was noted. The rate of wound infection was 5.8% [1].

## 7. Conclusions

Initial reports of neoadjuvant chemoradiotherapy were published over a decade ago; however, this treatment did not gain world-wide popularity. This might be due to the fact that most trials of neoadjuvant chemoradiotherapy were retrospective or single arm prospective trials, included a varied patient population, and differed in treatment regimens and aims. The surgical approach differs between the studies and some reports included a diverse population; thus, it was difficult to accurately measure the rates of curative local treatment for otherwise inoperable patients.

Reported data regarding neoadjuvant CT-RT is inconsistent, as different definitions of response were used, making it difficult to assess the true pCR rates after neoadjuvant combined therapy and whether pCR achieved by adding RT to neoadjuvant CT improved survival. Moreover, data of breast cancer subtypes, which is imperative in the decision of systemic therapy and dictates the response rate (including pCR) in the chemotherapy-based neoadjuvant setting, was lacking from most trials. The safety of preoperative CT-RT was reported to be reasonable, as some indicated that RT interruptions in the CT-RT protocol were negligible.

It seems that the available data from past neoadjuvant chemoradiotherapy trials do not correspond with the revolution in our understanding of unique breast subtypes and the implication of pCR on patient survival. Therefore, in our view, there is a place to re-evaluate, in selected cases, the role of chemoradiation in the neoadjuvant setting.

## Conflict of interest

No author has any conflict of interest to declare.

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