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Neoadjuvant Chemoradiation for Unfavourable Breast Cancer Patients: A Prospective Cohort Study

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Abstract

Purpose: Reaching a complete pathological response (pCR) after primary systemic treatment (PST), specifically in the subgroup of patients with triple negative (TNBC) or HER2-positive tumors, is associated with a significant survival gain. The combination of chemotherapy and radiotherapy could increase this synergistic benefit.

Methods/Design: This is an unicentric prospective cohort study that is going to include 40 localized breast cancer patients (TNBC or HER-2 positive) T2N0 or higher to receive neoadjuvant chemoradiation based on Pertuzumab-Trastuzumab-Paclitaxel followed by anthracyclines in Her-2 positive patients and CBDCA-Paclitaxel based regimen followed by anthracyclines in TNBC patients. Chemoradiotherapy concomitance will be with CBDCA-Paclitaxel/Paclitaxel-Her-2 double blockage. Dose prescribed will be 40,5 Gy in 15 fractions of 2.7 Gy, five fractions a week, to whole breast and ganglionar levels I-IV and ipsilateral internal mammary chain when indicated with simultaneous integrated boost of de 54 Gy in 15 fractions of 3.6 Gy to primary breast and/or axillary tumor (highlighted by PET). The primary study endpoint will be to asses pathological complete response rates (pCR) and objective response (OR) rates. Secondary endpoints will include to asses metabolic response rates by 18FDG-PET-CT, locoregional control and disease-free survival rates, tolerance and viability and security of the surgery after preoperative chemoradiotherapy.

Discussion: Tools and results developed in this study are aimed at answering if preoperative chemoradiation improves pathological and objective response and ultimately improves survival rates, tolerance and viability of surgery in desfavorable breast cancer subtypes.

Keywords: Breast cancer; Chemoradiation; Neoadjuvant chemoradiation; Unfavourale phenotypes; Pathological response

Background

Breast cancer is the most frequently diagnosed neoplasm with 404,900 new cases (29.2% of the total) in the 28 countries of the European Union (EU-28), with an age-standardized rate of 113.6 cases per 100,000 women accounting for the largest number of predicted cancer deaths (98,800 deaths, 21.4/100.000 women, 15.9% of total) in 2018 [1].

Advances and improvements in the locoregional treatments of breast cancer, surgery and radiotherapy, have contributed decisively to decrease locoregional recurrences and distant recurrences while increasing breast-cancer and overall survival. The results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, conducted on 17 studies that included 10,801 women, demonstrated that radiotherapy significantly decreased the risk of recurrence, locoregional or distantat at 10 years, as well as breast-cancer specific mortality at 15 years. The same group published in 2014 an update of results with a greater follow-up including 8,135 women; the results showed a significant reduction after radiotherapy in the likelihood of locoregional and/or distant recurrence in those women presenting with tumor lymph node involvement. These benefits were observed in all subgroups of patients, both in patients with 1-3 affected lymph nodes and in those with metastases in more than 4 lymph nodes. The benefits observed at 10 years resulted in a significant increase in breast cancer survival at 20 years and were independent of the administration or not of systemic treatment. According to the authors, "one death from breast cancer was avoided at 20 years for every 1.5 recurrences avoided during the first 10 years after radiotherapy [2,3]. Furthermore, benefits of breast irradiation also encompass low risk or very low risk breast cancer patients, improving significantly overall survival rates [4].

However, and in spite of the good results observed in the last decades in regard to the increase in survival in women diagnosed with breast cancer, subgroups of patients still exist where the prognosis is more unfavorable.

Methods

TNBC and HER2-positive tumors, which globally represent less than 20% of the total breast cancer diagnoses, confer a worse prognosis. TNBC have a poorer short-term prognosis than other subtypes, in part because there are currently no targeted therapies for these tumors, and HER2-positive cancers tend to grow and spread more aggressively than other subtypes, especially when compared to hormonal sensitive breast cancers. Much of the research effort in

recent years in the treatment of breast cancer is aimed at finding effective therapeutic alternatives to more aggressive tumor subgroups. It is remarkable the development of specifically targeted treatments against HER2-positive tumors that have substantially changed the prognosis in this subgroup [5].

Neoadjuvant systemic treatment or primary systemic treatment (PST) for breast cancer was primary conceived to allow more conservative surgeries for those tumors initially considered unresectable, but its use has extended later to monitorize the tumour shrinkage and rapidly assess pathological and clinical responses. This strategy is of special interest in Her-2-positive and TNBC breast cancer patients, who are the best responders to neoadjuvant chemotherapy. Different studies have shown that reaching a complete pathological response (pCR) after PST, particularly in patients with TNBC or HER2-positive tumors, is associated with a significant survival gain [6-8].

This protocol of concurrent neoadjuvant radiochemotherapy is designed based on the hyphotesis that in the more aggressive tumor subgroups, TNBC and HER2-positive patients, pCR has been shown to be a surrogate survival marker.

Therefore, neoadjuvant strategies to increase rates of pCR could be associated with an improvement in final outcomes.

Protocol Design

Adult patients with non-metastasic breast cancer HER2-positive or TNBC will be offered to enrol this prospective, unicentric study of neoadjuvant concurrent radiochemotherapy. This study has received ethical approval from the Inhouse Local Ethics and Clinical Committee (Code: 18.12.1241E1-GHM). Participants enrolled in this protocol provide their written informed consent prior to their inclusion.

Objectives

The primary study endpoint will be to asses pCR rates and objective response (OR) rates after preoperative chemoradiotherapy.

Secondary endpoints will include to asses metabolic response rates in breast and/or nodal areas by 18FDG-PET-CT after preoperative chemoradiotherapy, locoregional control and disease-free survival rates, tolerance and potential toxicity of the combination of radiotherapy and chemotherapy in regard to potential cardiac toxicity when left breast is treated and to asses viability and security of the surgery after preoperative chemoradiotherapy.

Patient's Selection

All the patients with a proven diagnosis ofTN and HER2-positive breast carcinoma will be evaluated by a multidisciplinary breast tumor board to determine the benefit of their inclusion in the study.

Inclusión criteria are restringed to women over 18 years-old, presenting with a measurable breast tumor clinically staged as T ≥ 1N+ or T ≥ 2N0, adequate performance status (WHO ≤ 2), adequate bone-marrow reserves (WBC count before treatment>1500/mm^3, platelets count>100000/mm^3 and hemoglobin>10 g/l) and cardiac function (LVEF ≥ 50%).

However, patients with previous history of cancer, metastasic breast cancer at diagnoses, previous chemotherapy, uncontrolled cardiovascular or lung diseases, uncontrolled neurological or psychiatric diseases, presence of neuropathy or basal levels of creatinine above 2 mg/dl, existence of diseases that contraindicate radiotherapy as well as pregnant women and those unable to understand protocol will not be enrolled.

Molecular Studies

Patients undergo both MRI and 18-FDG-PET-CT pre- and post-chemoradiation. Koo et al. demonstrated in a retrospective study of 548 patients that triple negative and HER-2 positive patients had higher SUVmaxvalues than luminal ones in 18FDG-PET-CT [9] and could help in the tumor contourning process for radiation treatment in the same way as it is validated in other tumor sites as head and neck or haematological tumors. Also, 18FDG-PET-CT allows to evaluate the heterogeneity in the tumor which has been related to prognosis [10] and have been used to predict response to neoadjuvant treatment in breast cancer patients [11].

However, studies that compare both techniques show that MRI is more specific and precise than PET but less sensible to identify patient that respond compared to those who do not [12].

Cardiovascular Assessment

An excess of concern about cardiovascular toxicity could avoid receiving potential curative oncological assistance, however, underestimate this risk could compromise long term vital prognosis. Cardio-oncology guidelines establish that cardiovascular toxicity is widely recognized, however there is lack of scientific evidence in the cardiovascular complications' management of these patients since they have been systematically excluded of clinical trials [13]. A multidisciplinary approach, including analysis of cardiovascular risk factors, socio-demographic variables and functional cardiological evaluation during treatment and on follow-up period would be of great interest to demonstrate the safety and reliability of the combined treatment.

Treatment Procedure

The study flowchart is presented in Figure 1. Pre-treatment appraisal included axillary evaluation. In clinically negative nodes (cN0), a selective biopsy of the lymph node prior to the start of radiochemotherapy is recommended in order to evaluate lymph node response to treatment in the case of a positive sentinel lymph node. In patients with suspected lymph node involvement by imaging (US, PET), histological confirmation should be performed by using FNA and image-guided marker-clip placement in positive axillary lymph node prior to the start of radiochemotherapy. After radiochemotherapy, ALND will be performed in all cN+patients regardless of the response to treatment.

Once fulfilled inclusion requirements, patient undergo radiotherapy simulation in an 18-FDG-PET-CT with both arms raised on an immobilization device. RayStation® (RaySearch Laboratories AB, Stockholm, Sweden) planning system will be used for import, contourning and clinical radiation dosimetry. Conformal 3D or more complex VMAT will be used according to constraints acomplishment. Treatment will be delivered in an Elekta VERSA HDTMlinac with 6 and or 15 MV photons plus 6 degrees of freedom couch Elekta HexaPODTM (Elekta AB, Stockholm, Sweden). Dayly repositioning

will be verified by VERSA X-ray cone-beam CT andCatalyst HD (C-RAD, Uppsala, Sweden) systems.

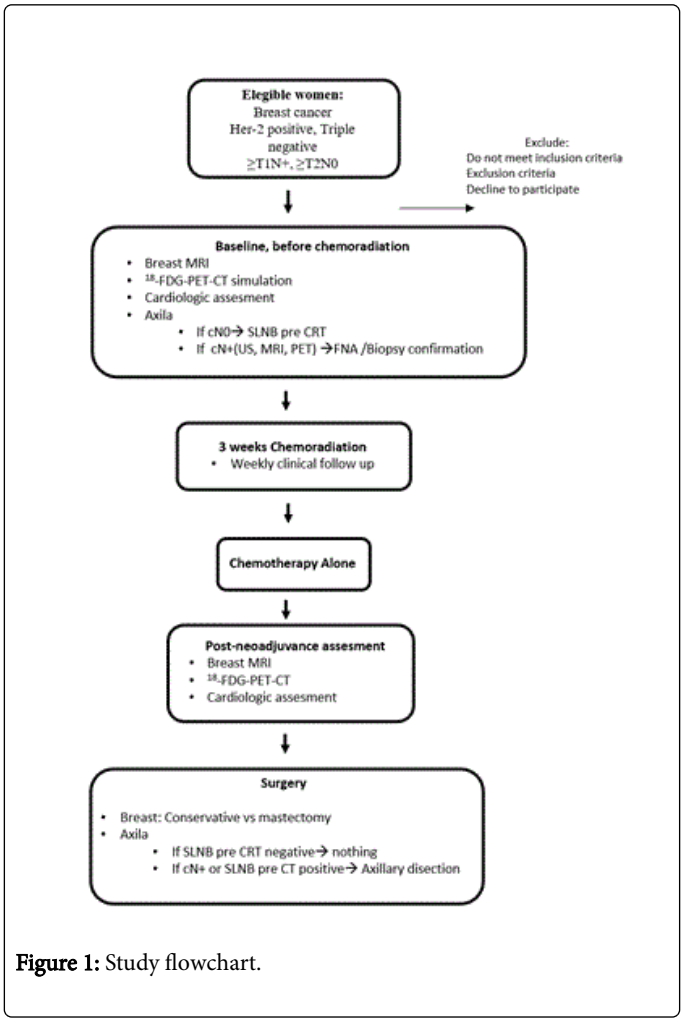

Figure 1: Study flowchart.

Dose prescribed will be 40,5 Gy in 15 fractions of 2.7 Gy, five fractions a week, to whole breast and ganglionar levels I-IV and ipsilateral internal mammary chain when indicated, with simultaneous integrated boost of de 54 Gy in 15 fractions of 3.6 Gy to primary breast and/or axillary tumor (highlighted by PET). Dose bioequivalence has been calculated with Linear quadratic Model (LQM), based on dose per fraction, total dose, number of fractions and α/β value of 4 for tumor control (BED= nd [1+d/(α/β)] [14,15]. Thus, equivalent doses at 2 Gy/fraction (EQD2Gy) are 68.4 Gy for macroscopic tumor (defined according to MRI/PET-CT) and 45.2 Gy for remaining breast and axillary lymph-node areas.

Concurrent chemotherapy for HER2-positive will consist of 4 courses of trastuzumab (6-8 mg/m^2), pertuzumab (420-840 mg/m^2), and paclitaxel (80 mg/m^2) each 3 weeks followed by 3 courses of fluoruracil-epirubicin-ciclofosfamide (500 mg/m^2-75 mg/m^2-500 mg/m^2) and trastuzumab every 3 weeks for a whole year.

For those patients with TNBC tumors, concomitant chemotherapy wil include 4 courses of paclitaxel (80 mg/m^2) on days 1, 8 and 15 plus carboplatin (AUC 2) on days 1,8 and 15 each 3 weeks followed by 4 more courses of doxorubicine-ciclofosfamide (60 mg/m^2-600 mg/m^2) every 2 or 3 weeks according to haematologyc toxicity.

After finalization of chemotherapy, a new 18FDG-PET-CT and MRI will be performed to evaluate methabolic and radiological response. All the patients will undergo surgery, either mastectomy or conservative approach, with proper axillary evaluation as previously defined. Type of surgery will be decided according to each individual patient and the clinical and metabolic response achieved after neoadjuvant treatment.

Clinical follow-up will be similar to those patients not included in this treatment protocol. Every 3 months the first two years, every 6 months between the second and fifth and annual therefore.

Statistical Analysis

This is an observational prospective study. Regarding the incidence and the historical capacity to enroll HER-2 positive and TNBC breast cancer candidate to neoadjuvancein our hospital, we estimated that we were recruiting 40 patients in 24 months. The follow up after surgery is two years.

Microsoft Excel v 19.0 is going to be used for descriptive analysis and IBM SPSS Statistics software for survival curves and analysis of data.

Status of the Study

The study is currently recruiting patients.

Results and Discussion

Survival among women with breast cancer has been found close related with the immunohistochemical profile, and those tumors with HER2 gene overexpression or TNBC had lower survival rates. However, despite of the HER2 gene overexpression is a negative prognosis factor, the extended used of trastuzumab is changing the natural history of these patients. Thus, trastuzumab and other targeted therapies for HER2-positive breast cancer have been clearly shown to improve survival, although TNBC tumors still have a poorer prognosis compared to ER-positive subtypes.

Theses evidences indicate a need to perform clinical trials accounting for different strategies against different cancer subtypes. The concomitant administration of chemotherapy and radiotherapy before definitive surgery offers the possibility of exploring alternatives in the treatment of the most unfavorable breast cancer subgroups that allow improving the results of the treatment and the final prognosis of these women.

Rationale for simultaneous chemotherapy and radiotherapy:

Radiation therapy is a mainstay of breast cancer treatment because achieving an adequate locoregional control is a cornerstone to improve the final outcome of breast cancer. About eight out of ten patients with this type of tumour are treated at some point with ionizing radiation. Radiotherapy improves locoregional control and even long-term survival in breast cancer patients both after breast conserving surgery or mastectomy [3,4,16]. Although HER2-positive and TNBC tumors were associated with an increased risk of LRR [17], published evidences show that all molecular subtypes of breast cancer benefit from the administration of radiotherapy [18-20].

Currently, neoadjuvant administration of systemic therapy is common for breast cancer patients with unfavorable subgroups in an attempt to achieve high rates of pCR since it has been associated in

both, HER2-positive and TNBC, with an improvement in the final results [6-8].

At least three phase III studies (MD Anderson Cancer Center neoadjuvant trastuzumab trial, Neoadjuvant Herceptin (NOAH) trial, GeparQuattro trial) compared neoadjuvant chemotherapy alone to same chemotherapy plus Trastuzumab and showed a significative increase (65%) of pathological complete response [1].

Furthermore, large randomized clinical trials demonstrated that dual HER2 targeted blockage with trastuzumab/lapatinib and trastuzumab/pertuzumab works synergisticly. The Neosphere study analyzed the combination of trastuzumab and pertuzumab plus chemotherapy in HER2-positive patients. The significative increased of pCR and the impact in survival rates positioned this combination as the new standard [21-23]. The Tryphaena study assesed the differences between distinct chemotherapy schemes when combined with double Her-2 blockage reaching pCR in 57%-66% of patients without observing any variations directly attributable to chemotherapy schedule [2,3]. Finally, the Berenice study based on the combination of neoadjuvant pertuzumab, trastuzumab and anthracycline-taxane based chemotherapy reached the same pCR rates described previously confirming again security in terms of cardiac tolerance [24].

On the other hand, women with TNBC disease still suffer the worst prognosis. Neoadjuvant systemic treatment has been also proposed as an attractive alternative for these patients given the known correlation between pCR rates and both progression-free and overall survival [4]. Furthermore, in last years addition of platinum-derived compounds to a classical taxane-anthracycline schedule improved this percentage over 50% [25].

Thus, achieving a high rate of pCR has become a priority objective of the neoadjuvant systemic tretament of breast cancer, especially in the most unfavorable subgroups. Interestingly, radiation therapy benefits in both locoregional free survival and disease-free survival and its independence of the pCR status reached after neoadjuvant chemotherapywas demonstrated by a metanalysis of 3,481 patients included in GeparTrio, GeparQuattro and GeparQuinto [5,26].

Although frequent in other tumors where concurrent delivery of chemotherapy and radiotherapy is widely practiced (i.e. head and neck, esophagus, stomach, rectal, uterine cervix or lung cancer) showing an increase not only in local control but also in survival rates, this combination has not been a widespread practice in breast cancer patients. In spite that surgery followed by chemotherapy and radiation later is considered the more conventional approach to breast cancer multidisciplinary treatment, the increasing use of neoadjuvant treatments has renewed the interest in exploring combination of chemotherapy and radiation therapy in breast cancer, especially in the most aggressive and unfavorable molecular subtypes

A recent update of a study that included 105 women with breast cancer treated with concurrent chemoradiotherapy with paclitaxel administered two days a week showed a high rate of pCR, especially in the subgroup of TNBC patients and in those positive HER2 with no positivity for estrogen receptors, where they reached 54% and 50% pCR, respectively [27].

Overall, this and other studies of concurrent radiochemotherapy in breast cancer have shown a rate of OR of 64%-93% and pCR of 16%-47%. But not only the improvement in local control, but also the possibility of making operable tumors considered unresectable at the start positively impact survival rates. These evidences support the hypothesis that the effects of radiotherapy are complementary to those of chemotherapy and that the combination of both therapies may be beneficial in women with locally advanced breast tumors [28].

Finally, the prolonged duration of the different treatments is one of the factors that negatively influence the comfort and quality of life of the patients. The results of 2 randomized studies confirm that the use of shortened radiotherapy schemes in breast cancer increases the quality of life of patients and improves comfort and satisfaction with treatment by decreasing the total duration of the treatment [6-8]. The simultaneous administration of radiotherapy and chemotherapy also allows reducing the total duration of treatment and the number of visits to the hospital, which can contribute to improve patient satisfaction and therapeutic adherence while facilitating the reduction of the total treatment costs. Table 1 reflects published results of different treatment schedules including concurrent administration of chemotherapy and radiotherapy in localized breast cancer. The rates of pCR vary between 17% and 45%, but reaching more than 50% in patients with tumors of the most unfavorable subtypes, HER2-positive and TNBC, when taxanes and targeted therapies were used in combination with local radiotherapy [29].

Safety of concurrent chemotherapy and radiotherapy for breast carcinoma:

The existing experience in the use of preoperative radiotherapy in localized breast cancer has shown that this therapeutic alternative is feasible, well tolerated and associates complete pathological response rate of 8%-11% [9]. Recently, results based on the analysis of the large the SEER (Surveillance, Epidemiology, and End Results) databases have been published showing that preoperative radiotherapy in breast cancer is safe and without decrement in overall survival in patients with localized tumors [30]. Nevertheless, despite of existing evidences, concerns have raised about security of simultaneous administration of chemotherapy and radiotherapy in breast cancer, and more specifically regarding to the use of potential cardiotoxic drugs such as trastuzumab or pertuzumab. Preoperative and postoperative combination of radiotherapy and taxanesis not only effective but also is secure. The synchronic delivery of a cardiotoxic agents as trastuzumab, pertuzumab or both together plus locoregonal radiotherapy has shown to be secure and well tolerated without increasing cardiac advers effects, not only with conventional but also with hypofractionated schemes even when internal mammary chain must be irradiated [10].

Advantages and future perspectives of preoperative concomitant chemoradiotherapy in breast carcinoma:

Irradiating the tumor preoperatively instead of the surgical bed is certainly more precise and accure and could associate some relavant advantages. First, rutinary use of PET and MRI images helps defining the target volume with high precision in contrast of the contourning of the surgical bed enclosed by fibrosis plus seroma and surgical clips that can change significantly. Second, new high conformal radiation techniques and systems to track corporal movements (SGRT, Superficial Guided Radiation Therapy) help minimizing dose in close healthy organs at risk and improving precision and security of treatments. Third, depending of initial stage or tumor location, some patients should undergo total mastectomy. It's a well-known fact that immediate breast reconstruction (IBR) improves psychosocial and quality of life outcomes, so administration of radiation therapy pre-operatively together to neoadjuvant chemotherapy, may reduce time to completion of treatment and facilitate better and faster access to IBR. Neoadjuvant radiotherapy has resulted in significant shorter time

between diagnosis and treatment completion and a significant higher proportion of patients undergoing neoadjuvant chemoradiation therapy underwent IBR without an increase in complication rate [31]. Likewise, the group of Grinsell et al. [11] evaluated feasibility of IBR after neoadjuvant chemoradiotherapy in 29 patients and also concluded that it is possible to perform immediate free autologous reconstruction after neoadjuvant chemotherapy and preoperative radiotherapy with excellent results and at least equivalent oncological efficacy. More focused in the type of reconstruction, a review of 40 patients with locally advanced breast cancer who underwent autologous IBR post neoadjuvant chemoradiotherapy, showed that the most common choice of flap was immediate deep inferior epigastric perforator (DIEP, 31), followed by transverse or diagonal upper gracilis (5), muscle-sparing transversus abdominis (3), and stacked DIEP (1). The rates of complications were similar to delayed reconstruction. Authors conclude that this treatment sequence allows patients to have an immediate gold standard reconstruction without an increase in surgical morbidity. It affords the benefits of IBR without concern in delaying adjuvant therapy and appears to be safe from an oncological perspective [12]. Fourth, the use of radiotherapy boost on tumor bed after whole breast radiation has showed in multiple randomized studies a significant decrease in local recurrence. The growing interest in the use of oncoplastic surgical techniques posing a challenge to localize tumor bed due to tissue rearrangement asociated to oncoplastic approaches, making dificult to administer radiation boost safely. Preoperative chemoradiotherapy would allow to administer radiotherapy, including the boost, with absolute certainty in the appropriate location regardless of the surgical technique subsequently used [31-34]. And fifth, evidences support the hypothesis that tumors develop multiple mechanisms of immune evasion as they progress, with some cancer types being inherently better at 'hiding' than others. It has been suggested that radiotherapy applied to the large bulk of tumor activates a robust antitumor immunity, a fact that would be absent when radiotherapy is administered after surgery, and this radio-induced immunity could contribute to eliminate not only the primary tumor but also microscopic foci present in the ipsilateral and contralateral breast as well as diminishing the risk of distant micrometastasis, leading to an abscopal effect of preoperative radiotherapy that could even be enhanced by the addition of systemic agents, such as concurrent administration of taxanes [13].

With an increased understanding of tumor immune surveillance of breast carcinomas, immunotherapy has emerged as a promising treatment strategy despite historically being thought of as an immunologically silent neoplasm [35]. The causes of breast cancer's immune silence derive from mechanisms that diminish immune recognition and others that promote strong immunosuppression. Tumors that show greater immunogenicity and have greater infiltration of immune cells tend to be an indicator of response to chemotherapy and good prognosis, especially in TNBC and HER2-positive breast cancers [36,37]. Increasing evidence demonstrates that radiation acts as an immune stimulus, recruiting immune mediators that enable anti-tumor responses within and outside the radiation field (known as the abscopal effect). According to these, an attractive approach for unfavourable breast cancers could be preoperative combination of radiotherapy, chemotherapy and immunotherapy searching for an optimal pCR rates, at least in TNBC and HER-2 positive breast cancer (Table 1).

Author	Patients	Treatment	% Pathological response	5-Year disease free survival	5-Year overall free survival
Formenti, et al. [14,15]	35	Concurrent RT-5Fu/S/AC adjuvant	35%	58%	pCR 90% others 65%
Skinner, et al. [3,4,16]	30	Concurrent RT-5FU/S	pCR 17% (objective response 73%)	NA	NA
Skinner, et al. [17]	29	Concurrent RT-Paclitaxel/S	pCR 26% (objective response 89%)	NA	NA
Chakravarthy, et al. [31,34,38-45]	38	Concurrent RT- Paclitaxel	pCR 34%	NA	NA
Bollet, et al. [18-20]	60	Concurrent RT-Vinorelbine-5FU	pCR 27%	83%	88%
Shanta, et al. [46,47]	1117	Concurrent RT- CMF-ECF-FAC	pCR 45,1%	64.5%	75.6%
Alvarado- Miranda, et al. [47]	112	Concurrent RT- Mytomicin +5Fu or RT- Gemcitabine-CDDP	pCR 29,5%	76.9%	84.2%
Adams, et al. [6-8]	105	Concurrent RT- Paclitaxel +/- Trastuzumab/S/ Doxorrubicine based chemo	34% RRHH neg (54%) Her-2+ (50%) RRHH+ (18%)	61.4%	71.6%
Matuscheck, et al. [21-23]	315	Concurrent RT-EC/CMF/AC/Mito xantrone/	pCR 29,2%	NA	NA

Table 1: Summary of studies of concurrent chemoradiation in breast cancer.

Conclusion

The treatment of breast cancer is in continuous evolution. Advances in breast cancer knowledge are leading to the development of new strategies adapted to the particular characteristics of the tumor. The combination of surgery, radiotherapy and systemic treatments remains the cornerstone of modern treatment of breast cancer. However, the temporal sequence of the combination is evolving and increasingly adapted to the tumor subgroup, always seeking to maximize the therapeutic effect of each of the modalities. The simultaneous administration of chemotherapy and radiotherapy before surgery may be an opportunity to improve the results particularly in those more unfavorable tumor subgroups, such as HER2-positive and TNBC.

Compliance with Ethical Standards

Conflict of interest

All the authors declares that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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