Review



# Breast Cancer Adjuvant Radiotherapy and Chemotherapy Sequencing: Sequential, Concomitant, or What Else? A Comprehensive Review on the Adjuvant Combinations Journey

Grazia Lazzari *, Ilaria Benevento, Antonietta Montagna, Barbara D'Andrea, Antonella Bianculli, Giovanni Calice, Raffaele Tucciariello, Giovanni Castaldo, Vito Metallo, Angela Solazzo

Posted Date: 6 September 2024

doi: 10.20944/preprints202409.0412.v1

Keywords: adjuvant chemotherapy; radiotherapy; concomitant RT ; sequential RT; timing

 doi:10.20944/preprints202409.0412.v1



*Review*

# Breast Cancer Adjuvant Radiotherapy and Chemotherapy Sequencing: Sequential, Concomitant, or What Else? A Comprehensive Review on the Adjuvant Combinations Journey

**Grazia Lazzari *, Ilaria Benevento, Antonietta Montagna, Barbara D'Andrea, Antonella Bianculli, Giovanni Calice, Raffaele Tucciariello, Giovanni Castaldo, Vito Metallo and Angela Solazzo**

Grazia Lazzari MD, Radiation Oncologist. Radiation Oncology Unit, Oncology Research Institute of Basilicata-IRCCS-CROB, Rionero in Vulture (PZ), 85028 Italy

* Correspondence: lazzarigrazia@gmail.com

**Abstract:** Up to now in breast cancer (BC) treatment, adjuvant chemotherapy (A-CT) precedes adjuvant radiotherapy (A-RT). It's beyond question that A-RT improves local control while A-CT improves the Disease Free Survival (DFS) due to the reduction of metastatic distant recurrences. Taken togheter these two approaches impact favourably on the reduction of breast cancer mortality. In the last twenty years, the adjuvant treatment of BC has evolved quickly due to a better knowledge of its molecular biology , genetic prohile and its $\alpha/\beta$ ratio 3 / 4 Gy for the tumor and normal tissues radiosensitivity. Thus new schedules with hypofractionated radiotherapy have been tested and third generation of A-CT have been introduced leading to a better survival rate but a further delay in A-RT starting, raising the question to rethink the sequencing between these two approaches. However the sequencing timing between these two approaches still remains unchanged with A-CT before A-RT as the standard of care. Many attempts have been provided in order to optimize this sequencing. This comprehensive review is a journey among randomised, retrospective and prospective studies which highlights the past, the current and the novelties on timing sequencing proposals between these two modalities to assess the state of art. Sequential, concomitant and sandwitch modalities of chemotherapy with conventional or hypofractionated RT schedules from the most important studies will be analysed in this review.

**Keywords:** adjuvant chemotherapy; radiotherapy; concomitant RT ; sequential RT; timing

## 1. Introduction

### *1.1. Breast Cancer Adjuvant Therapy and "Killing Time " Factor*

Currently the standard sequencing in BC adjuvant treatment is chemotherapy followed by postoperative radiotherapy since the Upfront-Outback trial publishing [1,2]. Although data on toxicity, event free survival, distant metastases free survival, overall survival between the two arms ( RT-CT vs CT-RT) were similar and then confirmed in the ten years up-date, the arm CT-RT was chosen as the standard approach. Nowadays, the overall adjuvant treatment time has been revolutioned due to novelties in A-CT schedules and A-RT fractionations. In regard to A-CT, the introduction of third generation chemotherapy combinations has achieved a better breast cancer survival with a 20% reduction of breast cancer mortality in comparison with the second and first ones. The cost to pay is a time span lengthening to complete the entire course over 12 weeks due to more related toxicities [3]. By the other hand, radiation fractionation schedules have been shortened, equally effective with longer fractionation regimes, leading to a better compliance and quality of life, advantages in patients logistics, waiting lists and healthy system costs. In fact, Canadian trial, START

 doi:10.20944/preprints202409.0412.v1



trials, Fast Forward and HAI-5 trial, all of them, have assured long term local control and survival rate similar to the standard long course 2 Gy daily fractionation with no differences in normal tissue toxicity and a better compliance reported by the patients [4]. Thus is time to rethink the sequencing? [5].

*1.2. IORT Boost: A Teaching Lesson on the Role of Killing Time*

Radiation starting time is a key factor for cancer local control [6]. In turn, local control impacts on the long term survival benefit as emphasized by the comprehensive analysis of the complete DBCG 82bc study [7]. How can that happen in BC adjuvant treatment?

It is well acknowledged that after surgery a micro-metastatic migration from the tumor site in the blood may occur as the first step ; thus the tumour bed has been considered as a hub for several metastatic processes like the epithelial-to-mesenchymal transition (EMT) of tumour cells in the vessels. [8,9]. Consequently an early local RT is helpful to stop this migration, as showed by studies conducted on IORT boost models [10]. In fact data from Belletti et al have shown the anticancer radiation induced response of IORT boost in blocking the proliferation and migration of cancer cells in the fluid taken from the irradiated wound of patients treated with anticipated boost. To explain this effect, thereafter they investigated the effects of RT in the modulation of MicroRNAs (miR) in vivo human tissues [11]. MiR are small, non-coding RNA molecules with tissue specific expression found in animal serum/plasma with the function to regulate gene expression post-transcriptionally [12]. In BC patients treated with lumpectomy and IORT-boost, the analysis of MiR expression profiles on breast tissues from IORT-treated BC patients, showed how IORT is capable to modify the inflammatory wound response through the expression of miR-223 in the peritumoral breast tissue. This response consisted of a down regulation by miR-223 of the local expression of epidermal growth factor (EGF), leading to a decreased activation of EGF receptor (EGFR) on target cells as a consequence of the positive EGF–EGFR autocrine/paracrine effect induced by the post-surgical wound-healing response. In a second step on mouse model of BC, both RT-induced miR-223 and peri-operative inhibition of EGFR was able to inhibit the BC cell growth and reduced the recurrence proliferation in the transplanted BC mice. Thus there is a temporal window from surgery to recurrence in the adjuvant time in which a prompt RT exherts several molecular effects that is more than a simply direct killing of residual tumor cells. This window needs to be still covered by proper adjuvant sequencing between chemotherapy and radiotherapy.

**2. The Gap From Surgery to RT Starting**

The optimal gap between surgery and adjuvant radiation and chemotherapy is still a controversial matter since the definition of a killing time principle declarad by Mackillop WJ in an editorial in 1996 [13]. His famous slogan was " delays in RT should be As Short As Reasonably Achievable" in the ASARA motto, but this target in BC adjuvant therapy is still lacking. Looking back in time, a general perception on the adverse or unrelated survival outcomes between prolonged interval from surgery and RT starting has grown different evidences based on studies and populations so heterogeneous and treated with different chemotherapy schedules, (today obsolete) to draw definitive conclusions on the effective timing of RT.

*Trials and Population Based Studies: Early or Delayed A-RT?*

At the beginning of 90'years, the general policy in adjuvant approach was to maximize the use of chemotherapy prior to radiotherapy starting because of several theories on the systemic spread of BC at diagnosis, thus chemotherapy should not have only provided a systemic benefit but it should have also induced a local control due an anti-proliferative effects on any residual disease in surgical area [14].

However a widespread disappointing perception that delayed radiotherapy could have had a deleterious outcome in high risk BC patients was growing so why several retrospective and then randomized trials were designed on this issue. In a retrospective study conducted on 295 BC

 doi:10.20944/preprints202409.0412.v1



receiving not randomly CMF or anthracycline based chemotherapy and radiotherapy, results confirmed this intuition. In fact in the BC patients who received RT within 16 weeks after surgery, the actuarial 5-year local failure rate was 5% versus 35% in the patients irradiated more than 16 weeks after surgery. The 4-year crude incidences were 4% and 12% respectively (P = .06) [15].

In 1993 a retrospective study conducted by Bucholz, again assessed that a delay of adjuvant RT starting over 6 months from diagnosis resulted in a higher local failure rate. Furthermore, an increased rate of distant metastases and a decreased overall survival rate were recorded . In this study the population was divided into two groups based on the RT timing delivery. In the early radiation group, BC patients had A-RT within 6 months from diagnosis while in the delayed radiation group, patients received a delayed A-RTafter for more then 6 months from diagnosis due to more intensified chemotherapy regimes The chemotherapy schedules used in both groups were similar. Radiotherapy was delivered with standard fractionation. The best results were recorded in the early radiation group showing 98% of 8 year actuarial rate for local control vs 76%, p = 0.004, 80% overall survival vs 52%, p = 0.01 6 and 71% vs. 48% for the disease-free survival, p = 0.088. In the multivariate Cox regression model these significant differences were confirmed [16].

Thus the perception that delayed radiotherapy could have had a deleterious outcome in high risk BC patients raised the need to set up a formal randomized trial. In the mean time, in 1996 within two randomized trial using concurrent CMF in node positive pre/perimenopausal BC patients (IBCSG trial VI) and in node positive postmenopausal patients (IBCSG trial VII), this issue was assessed for the first time. In the IBCSG VI trial patients were randomised to receive CMF as follows: for either three consecutive courses on months 1-3, or six consecutive courses on months 1-6, both with or without reintroduction CMF . In the IBCSG VII trial patients were randomised to to receive tamoxifen for 5 years, or tamoxifen for 5 years with three early cycles of CMF, both with or without three courses of delayed CMF. Overall 718 eligible patients were enrolled : 433 on trial VI, and 285 on trial VII. Radiotherapy was provided only on the breast with standard fractionation 50 Gy and 10 Gy boost with a delay of 4 or 7 months after surgery for pre/perimenopausal patients, and 2 or 4 months after surgery for postmenopausal patients due to CMF completion. As a result, the estimates for the 4-year crude local failures were 8 % and 9% (p= 0.61) for pre/perimenopausal patients receiving RT at 4 or 7 months after surgery, and 3% and 6% for postmenopausal patients treated with RT at 2 months or 4 months after surgery (p= 0.63). Thus a modest delay of RT after 4 to 7 months following breast-conserving surgery and CMF through these two randomized trials seemed acceptable for risk of worst outcomes[17].

Years later, van Maaren Marissa C et al analyzed the impact on 10-year disease-free survival (DFS) in a Dutch BC population-based cohort treated with adjuvant therapy according to Dutch guidelines which advised to start radiation therapy (RT) within 5 weeks after breast-conserving surgery (BCS). They identified a population named group 2 which included patients treated with chemotherapy, and compared chemotherapy before (BCS-chemotherapy-RT) and after RT (BCS-RT-chemotherapy). As a result, timing resulted not affecting survival in BCS-chemotherapy-RT. In BCS-RT chemotherapy, Distant Metastases Free Survival was higher for > 55 than < 42 days interval [18]. Who is right and who is wrong is still debated. Recently, an Ontario population-based study on 1028 women with stage I-II BC treated with adjuvant RT-CT has focused on the impact related to the delay of A-RT start. As a result, a delay in RT over 12 weeks from surgery or 6 weeks from the end of CT was related to a worst survival probability [19]. In the RT only group, a waiting time of 12 weeks or more from surgery to the start of radiation was associated to worse event-free survival after a median follow-up of 7.2 years (HR: 1.44; 95% confidence interval: 0.98 to 2.11; p = 0.07). For the group who received intervening adjuvant chemotherapy before RT, a waiting time of more than 6 weeks from completion of chemotherapy achieved a worse event-free survival after a median follow-up of 7.4 years (HR: 1.50; 95% confidence interval: 1.00 to 2.22; p = 0.047). Looking back the Upfront-Outback trial, in the conclusion paragraph, there the warning to rethink the sequencing between A-CT and A-RT in case of prolonged chemotherapy schedules [2]. And here we are. In this comprehensive review we will move through the most important studies assessing the best

 doi:10.20944/preprints202409.0412.v1



sequencing using the past and modern CT-RT combinations in terms of efficacy , toxicities, total adjuvant duration time in order to recognize if there is an optimal killing time in the era with third line A-CT and HF-RT new standard schedules.

## 3. First - Second Generation Chemotherapy and Conventional Fractionated Radiotherapy

### *3.1. Chemotherapy and Sequential Radiotherapy vs Radiotherapy and Sequential Chemotherapy*

Up to now A-CT followed by A-RT still remains the standard of care. This approach has been the first attempt to combine adjuvant chemotherapy and radiotherapy starting from the results of the trial published in 1996 and then updated in 2005. In this study 244 patients were randomized to receive CT before RT vs RT before CT [1,2]. Chemotherapy consisted of a 12 weeks therapy with 4 cycles of CAMPF repeated every 21 days. Radiotherapy consisted of 25-30 fractions with standard fractionation on the breast and nodal areas. In the first report of 1996, no differences in the 5years actuarial rates of cancer recurrence at any site and of distant metastases in the RT-first group and the CT-first group (p= 0.17) and (p=0.05), respectively were found. No differences in toxicity and in overall survival (p=0.11) occurred. The update at ten years, confirmed these praevious data showing no statistically significant difference in the rates of freedom from any event, freedom from distant metastasis, or overall survival and toxicity between the CT-first and RT-first arms. However, A-CT before A-RT was chosen in the clinical practice assuming that delayed radiation after 12 weeks of chemotherapy from surgery could not have had a negative impact on survival and local control outcomes. In the conclusions, authors declared to be not sure to confirm these results for longer chemotherapy regimens. Interestingly, the median interval between surgery and the start of RT was 36 days (5 weeks) in the RT-first group and 126 days (31 weeks) in the CT-first group. A gap of more than 16 weeks was recorded between the surgery and RT in 1 % of the RT-first group and 84 % of the CT-first group. The median interval from the first breast excision to the start of CT was 29 and 13 weeks in the RT-first and CT-first groups, respectively. The time to start CT was less than 16 weeks from surgery. See Table 1

**Table 1.** First - second generation chemotherapy and conventional fractionated radiotherapy.

| Authors | Study | Sequencing | Chemotherapy | Toxicity |
|---|---|---|---|---|
| **Recht/ Bellon [1,2]** | **Rand 240 pts** | **RT-CT vs CT-RT** | **CAMPF (4 )** | **No diff** |
| **Serin [20]** | **Retro 154 pts** | **CT conc RT** | **Mitx+5 FU + C (4-6 )** | **G3 skin4.5%** |
| **Bellon [21]** | **Retro 45 pts** | **CT conc RT** | **Taxanes** | **G3 skin 20% docetaxel** |
| **Burnstein [22]** | **Rand 40 pts** | **CT conc RT** | **Taxanes Wkl vs 4 cycl** | **G3 pneumonitis 25% Wkl** |
| **Sanguineti [23]** | **Prosp 47 pts** | **RT -CT vs CT-RT** | **CEF 14 vs CEF 21** | **No diff** |
| **Rouëssè [24]** | **Rand 638 pts** | **conc RCT vs seq CT-RT** | **C-Mitx-5FU vs CEF** | **G3-4 leucopenia(A) Cardiac (B)** |
| **ARCOSEIN [25]** | **Rand 716 pts** | **CT-RT vs Conc RCT** | **C-Mitx-5FU** | **No diff** |

 doi:10.20944/preprints202409.0412.v1



| | | | | |
|---|---|---|---|---|
| **Livi [26]** | **Prosp 60 pts** | **Conc RCT** | **AC/ EPI+CMF** | **G3 skin 8.9%** |

Legend : Rand= randomised; Retro= retrospective; Prosp= prospective; seq CT-RT= Ct and sequential RT; RT-CT = Rt and sequential CT; Conc RCT = concurrent CT -RT.

*3.2. Concurrent Chemotherapy vs Sequential Radiotherapy*

In these studies, according to the advances in novel drugs discovery at the end of 90' years, schedules containing mitoxantrone, taxanes, anthracyclines and the most used CMF have been delivered concurrently or sequentially with standard fractionated RT, indicating the advantages of the concomitant arm in terms of local control with several differences in toxicity.

A first study on concurrent treatment was proposed by **Serin** et al using an anthracenedione agent like mitoxantrone to reduce cardiac toxicity [20]. In this study 154 patients affected by stage I or II BC received conventional RT of 50 Gy in 25 fractions concurrently to chemotherapy. Chemotherapy consisted of 5-fluorouracil, mitoxantrone, and cyclophosphamide every 21days for 4 to 6 cycles. As toxicity, G 1 cutaneous toxicity occurred in 62.3% of the cases, and severe G 3 radiation dermatitis requiring temporary interruptions of therapy was found in 4.5% of patients. Only one case of G 3 acute cardiac toxicity was recorded.

**Bellon** et al presented a retrospective study on 45 high risk breast cancer patients treated with RT concurrently with taxanes (paclitaxel or docetaxel) [21]. Radiation was delivered to the chest wall or breast with doses ranging from 4680 cGy to 5040 cGy. A boost dose of radiation was provided to almost of them while nodal RT was delivered when indicated. Grade 3 acute skin toxicity was 20% in the docetaxel arm vs the paclitaxel arm ($p$= 0.04). With a median follow-up of 11 months, only one patient developed breast fibrosis. The use of taxanes concurrent to A-RT was officialized by **Burnstein** in a randomized trial on 40 BC patients [22]. Paclitaxel was delivered according to two schedules: 60 mg/m$^2$ weekly x12 weeks or 135-175 mg/m$^2$every 3 weeks x4 cycles. As a first result, weekly paclitaxel treatment at 60 mg/m$^2$ per week with concurrent radiation was the dose-limiting toxicity in 4 of 16 patients (25%) with one case of severe pneumonitis requiring steroids. On the contrary, dose-limiting toxicity was not recorded among patients receiving concurrent radiation with paclitaxel given every 3 weeks at 135-175 mg/m$^2$. However, G 2 radiation pneumonitis not requiring steroid therapy was seen in 2 of 24 patients (8%). No severe radiation dermatitis was observed in both paclitaxel schedules. Authors concluded that while concurrent treatment with weekly paclitaxel and radiation therapy was not adviceble, the concurrent arm with less frequent paclitaxel dosing schedule was defined less toxic although the possibility of pulmonary injury as side effect.

In the set of antracycline, a dose-dense intensification study with standard fractionated RT given sequentially or concomitantly was assessed by **Sanguineti et al** [23]. This study provided a mild RT dose-intensity (DI) to compensate gaps with 2.3 Gy per fraction in case of RT interruptions for toxicity. Forty-seven stage I-II breast cancer patients, after conserving surgery, were randomized to receive the CEF regimen delivered every two weeks (CEF14) or three weeks (CEF21). RT was applied to the residual breast to a total dose of 50 Gy in five weeks. Radiotherapy DI was expressed as the average total dose received each week defined as 'weekly dose-rate' (WDR). As a result, 98.8% of patients received a cumulative total dose of RT within ±10% of that planned. The type of treatment (CEF14 vs. CEF21) did not affect the probability of WDR < 9.5 Gy/wk. Regarding the CT-RT overlap, patients receiving more than two cycles of chemotherapy during radiotherapy had an increased risk of RT delay compared to other patients (RR = 3.74, 95% CI: 1.44-9.48, P = 0.0063).

**Rouëssè J et al** enrolled 638 BC patients in randomized trial providing two chemotherapy arms concurrent or sequential to standard fractionated radiotherapy. [24]. A arm consisted of 5-fluorouracil 500 mg/m$^2$, mitoxantrone 12 mg/m$^2$, and cyclophosphamide 500 mg/m$^2$ and concurrent RT. In B arm adjuvant CT with FEC regime and sequential standard RT were provided. Chemotherapy was administered on day 1 every 21 days for 4 cycles. **The** median treatment duration times were 64 days in A arm and 126 days in B arm , respectively. No significant difference in overall or disease-free survival were observed but a 5-year locoregional relapse-free survival in Arm A of 3% vs 9%; in Arm B (p = 0.01) was recorded. The increased risk of locoregional recurrence in B arm

 doi:10.20944/preprints202409.0412.v1



was 2.8-fold increased by multivariate analysis (p = 0.027). In A arm the most frequent acute toxic effect was febrile neutropenia with Grade 3-4 leukopenia. At 1 year , cardiac side effects like subclinical left ventricular ejection fraction events at 1 year were reported due to concomitant radiotherapy (p = 0.02).

In the **ARCOSEIN** trial 716 patients were randomized to receive CT and sequential RT versus concurrent RT using a CT regimen with mitoxantrone 12 mg/m², 5 fluorouraci500 mg/m², cyclophosphamide 500 mg/m² every 21 days for six cycles and standard fractionated RT. Adjuvant treatment started within 6 weeks after surgery. As a result, the 5-year DFS was 80% in both groups ( p = .83). Moreover no statistically significant difference in locoregional recurrence-free survival and OS were observed (p =.76 respectively). However, in the node-positive subgroup, the 5-year LRFS was improved in the concurrent arm (p= .02), corresponding to a risk of locoregional recurrence decreased by 39% (HR, 0.61; 95% CI, 0.38 to 0.93). Moderate acute locoregional toxicities were found in the two arms [25].

Two concomitant AC based regimes with standard RT study was conducted by **Livi** et al on 60 BC patients. Four cycles of AC (doxorubicin plus cyclophosphamide) vs four cycles of epirubicin (EPI) followed by four courses of iv CMF every 28 days were adopted. RT was appplied to the breast and nodal areas with 50 Gy mean delivered dose ( range 46–52 Gy). The boost dose was 10 Gy for patients with tumour-free surgical margins and 20 Gy for patients with positive margins. As a result, the concomitant treatment yelded 8.9% of acute skin G3 toxicity with one case of G4 toxicity (1.7%). RT was stopped in 21.3% of patients with a temporary RT delay of 5 mean 5 days. CT interruption of ≤7 days. was applied in 57.1% of patients because of haematological toxicity. An asymptomatic reduction of left ventricular ejection fraction >10% and <20% of the baseline value was recorded in both groups [26]. See Table 1

*3.3. CMF or AC (Concurrent vs Sequential RT )*

The CMF combination has been the most used treatment delivered concurrently to RT over AC schedule. **Faul et al** tested the efficacy of concurrent "standard" CMF vs iv CMF regimes in 116 BC patients with stage I-II BC treated with CMF and A-RT [27]. The standard CMF regime consisted of cyclophosphamide 100 mg/ m² os days 1–14, methotrexate 40 mg/m² i.v. days 1 and 8 and 5-fluorouracil 600 mg/m² days 1 and 8 repeated every 28 days for six cycles. The i.v. CMF regimen consisted of cyclophosphamide 600 mg/m2 i.v., methotrexate 40 mg/m2 i.v. and 5-fluorouracil 600 mg/m2 i.v. given every 21 days for 6 to 8 cycles. Radiotherapy was delivered according standard fractionation. In this study 73 patients were treated prospectively with concurrent therapy and were retrospectively compared with a matched group of 40 patients treated with sequential or sandwich therapy. Concurrent sequencing didn't influence the scheduled delivered RT and CT doses. No significant difference in acute skin reactions or complications between the two groups were recorded with a small and significant delay in RT delivery : 1.32 days (0-15) vs 0.36 (0-7 ) in the concurrent group (p=0.03). Sequencing had no significant impact on haematological toxicity. 'Standard' CMF impacted on treatment delivery more than i.v. CMF . In fact the RT delay was 2.2 days versus 0.26 (p=0.002), the percent of delivered chemotherapy was 93% versus 99% (P=0.000004). This study showed that iv CMF was safe when delivered concurrently with standard RT.

To confirm the safety of concurrent administration of CMF vs antracycline based regimen, **Fiets et** al reported on a prospective, non-randomized, comparative study on the acute toxicity of RT alone vs RT given concurrently (RCT) to doxorubicin-cyclophosphamide (AC/RT) or CMF (CMF/RT). Standard fractionated RT on breast, chest wall and nodal areas was applied [28]. Totally 112 patients received CT/RT as follows: 61 patients were treated with AC/RT and 51 with CMF/RT; 42 patients were treated with RT only as controls. As a result, patients treated with AC/RT and CMF/RT had significant higher incidences of high-grade toxiciy compared with those treated with RT only. The AC/RT scheme was associated with significant high-grade skin toxicity than CMF/RT. A less than 85% of the planned chemotherapy reduction dose was applied to 11% of patients and 17% of patients treated with RCT had an admission to hospital. Authors concluded that RCT administration yielded an unacceptably high level of acute toxicity mainly with AC regimen.

 doi:10.20944/preprints202409.0412.v1



At the same time, **Arcangeli et al** published results of a randomized trial on RT concomitant vs sequential iv CMFfor 6 cycles conducted on 206 elegible patients [29]. A-RT was applied only to the whole breast to a dose of 50 Gy in 20 fractions followed by an electron boost of 10-15 Gy to the tumor bed. Patients in the concurrent treatment group generally received one cycle of CMF before the RT starting course. Radiation therapy started within 2 months from the day of definitive surgery and concomitantly with the second CMF course in the concurrent treatment group. In the sequential treatment group, RT started 7 months after surgery, mainly at the conclusion of the last CMF course. All patients in the two groups received 100% of the planned dose. There were no RT breaks during the radiation time for skin or hematologic toxicity. All patients completed the planned radiotherapy and chemotherapy. No differences in 5-year breast recurrence-free survival ( (p 0.97), metastasis-free survival (p 0.44), disease-free (p 0.99) and overall (p 0.56) survivals were observed in the two treatment groups. Neither , no increased risk of toxicity was observed between the two arms. Authors concluded that iv CMF concurrent to RT , due to its advantage in shortening the overall treatment time could had been more useful to patients with high risk of recurrence, like those R1 surgical margins and with large tumor size.

In the prospective study of **Han et al,** 238 patients with stages I and II breast cancers were prospectively enrolled in a study with iv CMF concurrent vs sequential RT [30]. After BCS, all patients underwent iv CMF every 3 weeks for 6 cycles. RT on breast and nodal areas was delivered with standard fractionation with a 56 Gy median dose. In the sequential group, RT was started after the completion of 3 cycles of CT ; then additional 3 cycles of CT were delivered after RT. There was no significant difference in G3 or G4 hematologic toxicities during CT between the two groups. Neither a difference in RT related adverse effects was observed. During the median follow-up of 42 months, systemic recurrences occurred in 18 patients (13.5%) of the concurrent group and in 20 patients (19.1%) of the sequential group.

**Livi et al** in the same year showed a retrospective 3 arms study comparing 485 patients treated with conservative breast surgery, 6 courses of CMF and postoperative whole-breast RT vs 300 patients who received postoperative CMF only vs 509 patients treated with postoperative whole-breast RT only [31]. As a result, a G2 acute skin toxicity occurred in the concurrent group (21.2% vs. 11.2% of the RT only group, $p < 0.0001$). Local recurrence rate was 7.6% in CT/RT group and 9.8% in RT group; this difference was not statistically significant at univariate analysis (log-rank test $p = 0.98$). However, at multivariate analysis adjusted also for pathological tumor, pathological nodes, and age, the CT/RT group showed a statistically lower rate of local recurrence ($p = 0.04$).

A retrospective study on 244 BC patients treated by radical surgery or breast conservative surgery [32] was conducted by **Ismaili et al**. In this study two adjuvant schedules of chemotherapy concurrently given to radiotherapy were compared. In A group 110 BC patients received anthracycline based chemotherapy according several regimens. All cyclces were delivered every 21 days for 6 courses: AC 60 (doxorubicin 60 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$); FEC75 (5-fluorouracile 500 mg/m$^2$, epirubicin 75 mg/m$^2$, and cyclophosphamide 500 mg/m$^2$); iv FAC50 (5-fluorouracile 500 mg/m$^2$, doxorubicin 50 mg/ m$^2$, and cyclophosphamide 500 mg/m$^2$). The B group consisted of 134 BC patients receiving iv CMF every 21 days for 6 couses. .Conventional fractionated radiotherapy 50 Gy on the whole breast (or on the external wall) and/or on the nodal areas was provided. .As a result, after 76.4 months median follow-up , locoregional relapse occurred in 1 patient in the antacycline treated group and in 8 patients in the iv CMF treated group. The disease free survival and oveall survival after 5 years were not statical significant between the two groups (p = 0.136 and p = 0.428 respectively), However, the loco-regional free survival at 5 years was better in A group than the B group (98.6% vs 94% p = 0,033). The rate of G2 and G3 anaemia was 13.9% and 6.7% in anthracycline group and CMF group respectively (p = 0.009). Grade 2-3 skin toxicity in the was 4.5% in A group vs 0% in the B group B (p = 0.013). Thus antacycline treatment concurrent to RT was more effective and toxic. See Table 2

 doi:10.20944/preprints202409.0412.v1



**Table 2.** CMF or AC (concurrent vs sequential RT ) .

| Authors | Study | Sequencing | Chemotherapy | Toxicity |
|---|---|---|---|---|
| **Faul [27]** | **Prosp 116 pts** | **CMF conc RT** | **st CMF vs iv CMF** | **No diff** |
| **Fiets [28]** | **Prosp 112 pts** | **Conc CT** | **AC vs CMF** | **High grade with AC** |
| **Arcangeli [29]** | **Rand 206 pts** | **Conc vs Seq** | **iv CMF** | **No diff** |
| **Han [30]** | **Prosp 208 pts** | **Conc vs Seq** | **iv CMF** | **No diff** |
| **Livi [31]** | **Retrosp 485 pts** | **RT seq CMF vs CMF vs RT** | **iv CMF** | **G2 skin in RCT** |
| **Ismaili [32]** | **Retro 244 pts** | **Conc CT** | **Ac-CT vs CMF** | **G2-G3 skin /haemat in Ac-CT** |

Legend : st CMF = standard CMF ; iv CMF = intravenous CMF; AC = adryamicin + cyclofosfamide; Ac = antracycline based.

## 4. Third Generation Chemotherapy and Conventional Fractionated Radiotherapy

In this section the long course chemotherapy regimens using combinations of anthracycline and taxanes schedules reflects the routinary daily practice. Radiotherapy is still delivered with standard fractionation.

### *4.1. Concurrent Chemotherapy vs Sequential Radiotherapy*

In a randomized controlled trial by **Ying et al** 155 locally advanced BC patients after radical mastectomy were treated with a chemotherapy regimen FEC followed by docetaxel (FEC-D) and then randomized to concurrent or sequential A-RT [33]. Patients randomized in the concurrent (CCRT) group were treated with docetaxel. In the second arm radiotherapy was delivered after chemotherapy (SCRT). At 39 months median follow-up (range 16–62) , the 3-year local-regional recurrence-free survival in the CCRT group was 92.3% vs 81.8% in the SCRT group ( p=.046). There were no significant difference in 3-year disease-free survival and overall survival: 76.9% and 64.9% (p=.073) and 87.2% and 81.8% (p= .342) , respectively. The CCRT sequence yielded better outcomes in the pT3–4 pN1–3 cM0 subgroups. In fact, the 3 year local recurrence-free survival was 88.2% vs 69.4% in the SCRT arm ( p=.036). The DFS rate was 72.6 % the CCRT group vs 41.7 % (p=.049, respectively). No significant difference was observed in OS (79.4% vs 69.4%, p=.313). No differences were recorded in terms of haematologic and skin toxicities showing a G3- 4 leukopenia in the CCRT group of 29.5% vs 31.2 % in the SCRT arm (p=.858). Grade 1 -2 radiation skin reactions was 89.7% in the CCRT arm vs 88.3% in the SCRT arm (p=.548) .

A prospective feasibility study by **Ali Assan et al** was published on 43 BC patients treated with modified radical mastectomy or breast conservative surgery and long course adjuvant chemotherapy concurrent to RT [34]. Adjuvant chemotherapy consisted of 4 cycles AC followed by 4 cycles of paclitaxel 60 mg/m$^2$ weekly for 12 weeks and concurrent RT with standard fractionation. As a result, at a 36 months median follow up, the overall survival was 95% and disease-free survival was 92.5% respectively. No local relapse or radiation pneumonitis were assessed. However a delay in radiotherapy starting was accounted for 15% because of acute G3 skin toxicity (10%) or severe mucositis and wound gap (2.5%). At the last follow up, the cosmetic outcome score was found excellent score in 62.5% of the patients.

 doi:10.20944/preprints202409.0412.v1



*4.2. Sandwich Modality of CT-RT vs Sequential RT*

**Woo J et al** reported on a retrospective study with sandwich CT sequencing with radiotherapy [35]. In this study 200 BC patients with node positive disease were treated with 4 cycles of AC chemotherapy followed by taxanes as follows: four cycles of paclitaxel 175mg/m$^2$ or docetaxel 75mg/m$^2$ every 3weeks. The sandwich group consisted of 110 BC patients while 90 patients were treated as a control group that received RT after the whole CT course (four weeks after the last CT drug administration). In sandwich RT group, RT started four weeks after the last AC cycle. In three weeks after completion of RT , then the courses of paclitaxel or docetaxel were administered. The dose of irradiation was 50.4 Gy for the whole breast or chest wall and nodal areas. Boost 10 Gy on the tumor bed was provided. The gap between surgery and RT starting was 3.0±0.8 months in the sandwich group vs 5.5±1.2 months in the control group. At mean 105.4 months of mean follow-up time, the locoregional recurrencerate was 3.6% in the sandwich RT group vs 12% in the control group (p= 0.012); there was no signifcant difference in distant metastasis between the two groups (25% vs 17% , p= 0.220). In the multivariate analysis, the RT sequencing appeared as an important predictor factor for LRR (P= 0.017). Moreover, in the luminal A subtype, DFS improved vs non- A luminal subtypes ( p= 0.001 vs p= 0.670 ) in the sandwich RT group vs the control group. The sequencing did not impact in OS differences between A luminal and non-A luminal subtypes (p=0.150 vs p= 0.679).

## 5. Chemotherapy and Sequential Hypofractionated Radiotherapy

This approach is carachterized by the introduction of hypofractionated radiotherapy (HF-RT) with several schedules varying from 16/15 to 5 fractions with or without a boost (sequential or concomitant). In almost of these studies patients have received second or third generation chemotherapy schedules prior to RT. To remind, initially the use of HF-RT after adjuvant chemotherapy in 2011 was not adviced by the ASTRO consensus due to several uncertainties of unknown or unexpected toxicities [36]. Finally, in 2018 ASTRO guidelines provided no limitations in its use with any kind of adjuvant chemotherapy [37]. All studies on HF-RT have included patients treated with chemotherapy and sequential RT after at least two weeks off chemotherapy.

*5.1. First-Second Generation Chemotherapy Followed by Sequential Moderate Hypofractionated Radiotherapy: The Hypofractionated Trials*

In the **Ontario's** randomized trial, 622 patients received the experimental arm consisting of 266 cGy/fr x 16 fractions on the whole breast using 2-3D technique. In this arm, 70 pts received A-CT consisting of CMF given before RT. The use of systemic therapy didn't affect outcomes in terms of survivals and toxicity with the control arm as shown in the following 10 years update in 2010 [38].

The following **UK trials** tested three schedules of hyporactionated radiotherapy on breast and supraclavicular area, all of them after completion of A-CT. In the **START trial A**, 737 pts were randomized to receive 39 Gy in 13 frs while 750 pts received 41.6 Gy in 13 frs. Overall 534 patients received A-CT according to the current guidelines. RT started after a gap of two weeks chemotherapy off. Anthracycline containing regimen was prescrived in 70.1% for the group receiving 41.6 Gy arm and in 71.1% for the 39 Gy arm. Intavenous CMF was prescribed in 29.5% for 41.6 Gy and 26.7% for 39 Gy arm. Adjuvant taxanes were delivered to 9 pts in the 41.6 Gy arm , and in 4 pts in the 39 Gy arm [39] . **In the START trial B**, 1110 were allocated in the experimental arm receiving 40 Gy in 15 fractions. In this arm, A-CT was delivered in 233 pts with A-RT delivered after a gap of two weeks after chemotherapy off. Anthracycline-containing regimen was delivered in 58.4% of pts. CMF combination therapy alone was prescribed in 39.9% of pts. Only six patients allocated in this arm received an adjuvant taxanes [40]. In these three trials the outcomes by sequencing with adjuvant chemotherapy was not the end-point.

**De Antonio** et al proposed a randomised study enrolling 85 patients treated with 2.25 Gy/fr for 20 fractions to 45 Gy total dose , followed by a boost dose of 9 Gy in 3 fractions to the tumour bed vs the standard fractionated RT. Up front chemotherapy with CMF, EC, FEC were provided with

 doi:10.20944/preprints202409.0412.v1



hormone therapy given concomitantly to radiotherapy. The median treatment time spent was 29 days for HF-RT and 37 days for the conventional radiotherapy. RTOG acute skin toxicities as erythema were recorded in 85% of BC patients treated with hypofractionation and in 96% of patients treated with conventional fractionation ($p = 0.01$). In the logistic regression model, neither chemotherapy or breast volume and breast maximum dose had an impact on toxicity. After 6 months, late toxicity was 10% in the hypofractionation group and 15% in the conventional fractionation group, respectively ($p = 0.4$) resulting not statistically significant at Kaplan-Meyer method ( $p=0.17$). The risk of late toxicity at 12 months was 5.9% and 29.2% in the group treated by hypofractionation; this risk at 30 months was 8.2% and 10.6% in the group treated by standard RT, respectively.

**Hijal T** et al. showed results on a retrospective study in which 162 pts were treated with hypofractionated RT with or without adjuvant CT regimens with anthracyclines and taxanes. Radiotherapy consisted of 42.4 Gy in 16 fractions on the breast. The chemotherapy was delivered in 48% of the studied BC patients; this group received a boost to the tumour bed [42]. Grade 3 acute skin toxicity or higher was similar between the two groups : 2.1% in the chemotherapy group vs. 4.4% in the radiation-alone group ( $p = 0.67$). Grade 0 acute skin toxicty was not statistically different ($p=0.67$). At 16 months minimum follow up, late skin toxicity was no significant. Late G3 or higher skin toxicity was 2.1% in the chemotherapy group vs. 0% in the no chemotherapy group ($p = 0.30$ respectively). Excellent or good scores Cosmetic outcomes were similar in both groups ($p = 0.80$).

**Kouloulias et al**. retrospectively analyzed 116 breast cancer patients with T1- 2 N0 Mx treated with 3-D conformal radiotherapy to a total dose of 50.54 Gy or 53.2 Gy in 19 or 20 fractions according to stage, over 23-24 days with the last three to four fractions as a sequential boost [43]. Two chemotherapy schedules were used: EC followed by taxanes and CMF. The antracycline regimen consited of EC for 4 cycles every 2 weeks (wks), a 3 wks brake and then 4 cycles of taxotere every 3 wks. The second group received 6 cycles of CMF chemotherapy every 21 days. The EORTC/RTOG acute skin toxicity was not significant for chemotherapy ($p = 0.154$), neither for the radiotherapy fractions ($p = 0.47$). Although at univariate analysis, only chemotherapy was significantly related to the acute skin toxicity with $p = 0.05$, in the multivariate analysis,this effect was not confirmed .None of the patients during the 2-years of follow-up presented any locoregional relapse. In conclusion any type of chemotherapy combined with hypofractionated RT had a negative impact to acute skin toxicity.

These results were confirmed by **De Sanctis et al** in a prospective study on 510 pts treated with a chemotherapy regimen consisting of 3 cycles of Adriamicin 60 mg/m$^2$ and 3 cycles of Taxol 200 mg/m$^2$ followed by 3 cycles of CMF and sequential HF- RT with or without boost according to Ontario or UK-START trials [44]. The mean gap time between chemotherapy and radiotherapy was 2 months, ( range 6 days-3.8 months). No treatment interruptions were recorded for acute toxicity. Acute skin toxicity G1 was 61.3%, G2/G3 was 20.5%; G2/G3 was 4.3%. At univariate analysis significant factors related to late fibrosis were chemotherapy ($p = 0.04$), diabetes ($p = 0.04$) and boost administration ($p < 0.01$); but at multivariate analysis these effect were not confirmed . Only the boost administration was related to skin effect ($p = 0.02$).

In a single arm clinical trail **by Vijayaraghavan et al.** 67 pts after modified radical mastectomy were treated with anthracyclines plus taxanes followed by adjuvant HF-RT with VMAT or IMRT modality. Treatment resulted in grade 2 and higher acute radiation dermatitis in 11.9 % pts with one patient developing a grade 3 skin toxicity [45]. With a median follow up of 9 months there were no significant late toxicities.

### *5.2. Second-Third Generation Chemotherapy Followed by Ultra-Hypofractionated Radiotherapy*

**Hans Van Hulle et al** conducted two prospective clinical trials on a new accelerated fractionated radiation schedule in the NCT04098926 and NCT03121248. In both studies, more than 150 BC patients were treated with hypofractionated RT consisting of 5 fractions of 5.7Gy to the whole breast or chest wall to a 28.5 total dose (TD), 5.4 Gy on regional nodes to 27 Gy TD with a simoultaneous boost (SIB) of 6.2Gy or 6.5Gy (31 Gy and 32,5 Gy) when required. Chemotherapy always preceeded RT with a minimum gap of 3 weeks. Patients received EC for 4 cycles followed by

 doi:10.20944/preprints202409.0412.v1



12 cycles of paclitaxel and hormone therapy. As a result, the role of adjuvant chemotherapy was not an influencing factor on acute and late toxicity.

Going to recent years, the multicentre, phase 3, randomised, non-inferiority trial **FAST-Forward** was published during Covid-19 pandemic. In this trial, a total 4096 BC patients were enrolled. The trial provided three RT arms: 40 Gy in 15 fractions (over 3 weeks), 27 Gy in five fractions (over 1 week), or 26 Gy in five fractions (over 1 week) to the whole breast or chest wall. Nodal areas were also included. More than 1000 pts received adjuvant chemotherapy before radiotherapy. Chemotherapy schedules consisted of anthracyclines or taxanes regimens as per guidelines. No differences in acute and late skin toxicity rate was recorded among the arms [48].

## *6.* Concurrent Hypofractionated Radiotherapy and Chemotherapy

### *6.1. Concurrent vs Sequential CMF and Moderate Hypofractionated RT*

**Isaac et al** reviewed the records of BC patients who received adjuvant CMF, most of them with hypofractionated RT. In this analysis, 202 BC patients were treated with concurrent HF-RT while 47 patients received a sequential schedule CMF/HF-RT. Mastectomy was allowed in 64% of patients. Nodal involvement occurred in 88% of them [49]. HF-RT schedule was 2.5 Gy/f to 40.0 Gy in 16 fractions, without a boost. RT interruption or discontinuation for acute toxicity occurred in 4% of patients in the concurrent arm vs 0% in the sequential ($p = 0.36$) with G3 or G4 RT induced toxicity 1.5% and 2.1%, for the concurrent and sequential groups ($p = 0.57$ respectively,). The median relative dose intensity of chemotherapy for patients receiving concurrent CMF/RT was 0.87; in the sequential CMF/RT was 0.84 while in the CMF group alone was 0.85, ($p= 0.22$). Authors concluded that CMF given concurrently to moderate hypofractionated RT had a low rate risk of severe toxicity and it was considered as a good choise to propose in adjuvant regimen .

### *6.2. Concurrent Third Generation Chemotherapy to Moderate Hypofractionated Radiotherapy*

**Chen et al** defined a phase II trial on HF.RT with concurrent paclitaxel enrolling 44 patients in stage II and III breast cancer [50]. All had received breast-conserving surgery and 4 cycles of AC with further 4 cycles of paclitaxel 175 mg/m $^2$ every 3 weeks. Radiotherapy was delivered concurrently during the first two cycles of paclitaxel using 39.6 Gy TD in 22 fractions and a tumor bed boost of 14 Gy in 7 fractions. As a result, **the** 5-year actuarial rate of disease-free survival was 88%, and overall survival was 93%. At 75 months median follow-up, no radiation pneumonitis occurred. No significant changes in the diffusing capacity for carbon monoxide (DLCo) soon after radiotherapy ($p = 0.51$) or in the following follow up ($p = 0.63$) were recorded. Acute cosmesis score was related to the volume of irradiated breast tissue. Only two patients developed acute Grade 3 skin toxicity.

In the **CONCERT** study, 60 patients with stage II–III invasive BC were treated with adjuvant taxane-based chemotherapy and HF-RT 40 Gy in 15 fractions ± boost [51] . Regional RT was allowed without the internal mammary chain. RT started with the third cycle of an adjuvant taxanes given in a 3-weekly schedule or with the eighth cycle in a weekly schedule. Adjuvant taxane CT was delivered in 4 cycles of 3-weekly paclitaxel 175 mg/m2 or 12 cycles of weekly paclitaxel 75 mg/m2 after anthracyclines. All HER2 positive patients received adjuvant trastuzumab while in ER/PR positive BC patients, standard endocrine therapy was provided. As a result, 36 patients received 3-weekly paclitaxel regimen and 24 received weekly paclitaxel regimen. No G3 or G4 toxicity were recorded with any treatment interruption and CT-RT programme completion in all treated patients. The median ejection fraction pre and post CT-RT 6 months was 60% ($p = 0.177$). No cardiac and pulmonary disfunctions occurred. At a median follow-up of 34 months, the 3-year actuarial rate of disease-free survival and overall survival was 75% and 98.3%, respectively. Due to an acceptable toxicity profile, author concluded that concurrent adjuvant chemoradiotherapy in breast cancer should have been considered in order to shortening the overall treatment time with a good cost-effective benefit.

 doi:10.20944/preprints202409.0412.v1



## 7. Back to the Future: Moderate and Ultra Hypofractionated Radiotherapy and Sequential Third Generation Chemotherapy

Inspired to the UpFront- Out back trial[1,2], a novel approach using hypofractionated radiotherapy before third generation chemotherapy comes from a retrospective study published in 2024. Data on acute-subacute toxicities and on reduced gap in the overall adjuvant treatment time have been provided.

*Up Front Hypofractionated Radiotherapy to Third Generation Chemotherapy*

In this retrospective study, 45 BC patients were treated with third-generation A-CT after hypofractionated RT in 15-5 fractions in IMRT or VMAT modality. with or without sequential or simultaneous integrated boost (SIB) [52]. Up front Hypofractionated RT was adopted according the HY5 protocol and START B trial. AH-RT started 35 median days (5 weeks) after surgery (30–45 days). Third-generation A-CT was delivered as per clinical guidelines and started after 10 mean days (8–15 days) off RT. The median interval from surgery and chemotherapy was 8 weeks (6–12 weeks). The median duration for the entire adjuvant treatment was 35 weeks from the surgery (26–40 weeks), according to the RT and CT schedules. No differences in G2–G3 acute skin and lung toxicities between the two AH-RT arms and CT shedules were found at univariate and multivariate analyses ($p = .077$ and $p = 0.68$; 0.67 and 0.87, respectively). At 6 months, the cumulative incidence of G3 skin toxicity was 3 for AH-RT - 5 frs and 2.5% for AH-RT - 15 frs ($p = 0.672$), respectively. Lung toxicity was 3.2 % and 2.5 % ($p = 0.618$), respectively. These results repropose the theme of a new randomized trial to assess the sequencing in the time of ultra and moderate hypofractionated RT which has demonstrated several advantages in logistics, waiting list and healthy system costs.

## 8. Conclusions

Since 1991, the issue of which best sequencing time between adjuvant chemotherapy and radiotherapy in breast cancer has been focused on by many studies with the aim optimize the overall adjuvant treatment time, reduce toxicity and maximize the benefits in local control and disease free survival. Retrospective, prospective and randomized studies across the last 25 years have tried to find out the best approach according the available drugs and radiation knowledges of the time faculties. Schedules with AC alone or CMF have been replaced with more effective and complex combinations usong anthracyclines followed by taxanes schedules that delay RT starting over 12 weeks. By the data provided by the reported studies, this delay seems acceptable when considering the up front first-second generation of CT; but the impact of third generation chemotherapy in the RT starting delay is still unknown and again bring our doubts back twenty years ago as Bucholtz did [16]. Due to a better comprehension of $\alpha/\beta$ ratio for the tumor and the normal breast tissue, fractionated radiotherapy has completely changed. Nowadays moderate hypofractionated radiotherapy in 15-16 fractions is considered the standard fractionation. The ultra-hypofractionated in 5 fractions will replace it soon. The use of simoultaneous boost (SIB) with IMRT modalities is also a new attempt to shortening the RT delivery at all [53]. However, still radiotherapy follows chemotherapy while the concomitant approach is less valued. Thus considering the advantage of up front HF- RT in reducing the gap from surgery, the chemotherapy initiation and the overall adjuvant treatment time, the benefit on BC survival outcomes are ensured in line with the ASARA principle and the IORT boost as shown by Belletti and Iorio experiments as before [10–12]. Is it time to rethink the sequencing? Working in progress.

## References

1. Recht ,A.; Come, S. E.; Henderson, C.; Gelman, R.S.; Silver, B.; Hayes ,D.F.; Shulman, L. N.; Harris, J.R . **The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer.** N Engl J Med.1996 ; 334(21): 1356-61. doi: 10.1056/NEJM199605233342102
2. Bellon, J.R.; Come, S.E.; Gelman, R.S.; Henderson, I.C.; Shulman, L.N.; Silver, B.J.;Harris, J.R.; Recht, A. **Sequencing of Chemotherapy and Radiation Therapy in Early-Stage Breast Cancer: Updated Results of a Prospective Randomized Trial.** J Clin Onc. 2005; 23(9): 1934-1940. doi: 10.1200/JCO.2005.04.032

3. Denduluri, N.; Somerfield ,M.R.; Chavez-MacGregor, M.; Comander, A.H.; Dayao, Z.; Eisen ,A.; Freedman, R.A .; Gopalakrishnan, R.S.L.; Hassett, M.J.; King, T.A.; Lyman, G.H. ; Maupin, G.R.; Nunes,R .;Perkins, C.L.; Telli ,M.L.; Troudeau, M.E.;Wolff,A.C.; Giordanp, S.H. **Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update.** J Clin Oncol. 2020;39(685):93. doi:10.1200/JCO.20.02510
4. Meattini, I.; Becherini, C.; Boersma, L.; Kaidar-Person, O.; Marta, G.N.; Montero ,A.; Offersen, B.V.; Aznar, M.C.; Belka C, Brunt AM, Dicuonzo S, Franco P, Krause M, MacKenzie M, Marinko T, Marrazzo L, Ratosa I, Scholten A, Senkus E, Stobart H, Poortmans P, Coles CE. **European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selections and dose and fractionation for external beam radiotherapy in early breast cancer.** Lancet Oncol. 2022 Jan;23(1):e21-e31. doi: 10.1016/S1470-2045(21)00539-8.
5. Lazzari, G.; Rago, L.; Solazzo ,A.P; Benevento ,I.; Montagna, A.; Castaldo, G.; Silvano, G. **Adjuvant chemotherapy and hypofractionated whole breast cancer radiotherapy: is it time to rethink the sequencing?** Radiother Oncol. 2022;177(247):8. doi:10.1016/j.radonc.2022.10.012
6. Huang, J.; Barbera, L.; Brouwers, M.; Browman, G.; Mackillop, W.J. **Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review.** J Clin Oncol. 2003;21:555–563. doi:10.1200/JCO.2003.04.171
7. Overgaard M, Nielsen HM, Tramm T, Højris, I.;Grantzau ,T.L.;Alsner , J.; Offersen,B.V.; Overgaard, J. DBCG Radiotherapy Group. **Postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy. A 30-year long-term report from the Danish breast cancer cooperative group DBCG 82bc trial**. Radiother Oncol. 2022;170:4–13. doi:10.1016/j. radonc.2022.03.008
8. Formenti, S.C.; Demaria, S. **Local control by radiotherapy: is that all there is?** Breast Cancer Res. 2008;10:215. doi:10.1186/bcr2160
9. Thiery JP. **Epithelial–mesenchymal transitions in development and pathologies.** Curr Opin Cell Biol. 2003;15(740):6. doi:10.1016/j. ceb.2003.10.006
10. Belletti, B.; Vaidya, J.S.; D'Andrea, S.; Entschladen, F. ; Roncadin, M.; Lovat, F.A.; Berton, S.; Perin, T.; Candiani, E.; Reccanello, S.; Veronesi, A.; Canzonieri, V.; Trovò, M.G.; Zaenker, K.S.; Colombatti ,A.; Baldassarre, G.; Massarut, S. **Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding.** Clin Cancer Res. 2008;14(1325):–32. doi:10.1158/1078-0432.CCR-07-4453
11. Fabris, L.; Berton, S.; Citron, F.; D'Andrea, S.; Segatto, I.; Nicoloso, M.S.; Massarut, S.; Armenia, J.; Zafarana, .; Rossi, S.; Ivan, C.; Perin, T.; Vaidya, J.S.; Avanzo, M. ; Roncadin, M.; Schiappacassi, M.; Bristow, R.G.; Calin, G .; Baldassarre, G.; Belletti B. **Radiotherapy-induced miR-223 prevents relapse of breast cancer by targeting the EGF pathway.** Oncogene 2016; 35:4914-4926. doi:10.1038/onc.2016.23
12. Iorio, M.V.; Croce, C.M. **MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review**. EMBO Mol Med 2012; 4: 143–159 doi: 10.1002/emmm.201100209
13. Mackillop ,W.J. ;Bates, J.H.; O'Sullivan,B.; Withers, H.R. **The effect of delay in treatment on local control by radiotherapy.** Int J Radiat Oncol Biol Phys. 1996;34:243–250. doi:10.1016/0360-3016(95)02049-7
14. McGuire, W. L. ; Abeloff, M.D.; Hortobagyi, G. N.; Swain, S. M. **Oncology viewpoints: Treatment of Stage III breast cancer. Breast Cancer Res. Treat**. 1989; 13(3):225-235 doi: 10.1007/BF02106572
15. Recht , A.; Come, S.E.; Gelman, R.S.; Goldstein, M.; Tishler, S.; Gore ,S.M.; Abner, A.L.;Vicini, F.A.; Silver, B. Connolly, J.L. **Integration of conservative surgery, radiotherapy, and chemotherapy for the treatment of early-stage, node-positive breast cancer: sequencing, timing, and outcome.** JCO 1991; 9:1662-67. doi:10.1200/JCO.1991.9.9.1662
16. Buchholz, T.A.; Austin-Seymour, M.M.; Moe, R.E.; Ellis, G.K.; Livingston, R.B.; Pelton, J.G.; Griffin ,T.W. **Effect of delay in radiation in the combined modality treatment of breast cancer.** Int J Radiat Oncol Biol Phys.1993 ; 26(1): 23-35. doi: 10.1016/0360-3016(93)90169-v
17. Wallgren , A.; Bernier, J.; Gelber, R. D.; Goldhirsch ,A.; Roncadin, M.; Joseph, D. ; Castiglione-Gertsch, M. **Timing of radiotherapy and chemotherapy following breast-conserving surgery for patients with node-positive breast cancer. International Breast Cancer Study Group.** Int J Radiat Oncol Biol Phys .1996 Jul 1;35(4):649-59. doi: 10.1016/0360-3016(96)00186-1
18. van Maaren ,M.C. ; Bretveld, R.W. ; Jobsen, J.J. ; Veenstra, R.K. ; Groothuis-Oudshoorn, C.G.M.; Struikmans, H.; Maduro, J.H. ; Strobbe, L.J.A .; Poortmans, P.M.P.; Siesling, S. **The influence of timing of radiation therapy following breast-conserving surgery on 10-year disease-free survival.** Br Journal of Cancer . 2017; 117, 179–188 | doi: 10.1038/bjc.2017.159
19. Raphael, M.J. ; Saskin, R. ; Singh, S. **Association between waiting time for radiotherapy after surgery for early-stage breast cancer and survival outcomes in Ontario: a population-based outcomes study.** Curr Oncol. 2020 April:27(2) e216–e 21. doi: 10.3747/co.27.5629
20. Serin, D. ; Aimard, L.; Kirscher, S.; Brewer, Y.; Félix-Faure, C.; Vincent, P. ; Chauvet, B.; Reboul, F. **Adjuvant combined radiochemotherapy: a feasibility study of a new strategy in stages I and II.** Bull Cancer 1997 Mar;84(3):247-253. PMID: 9207869

21. Bellon, J. R.; Lindsley, K. L.; Ellis, G .K.; Gralow, J. R.; Livingston, R. B.; Seymour, M. M. A. **Concurrent radiation therapy and paclitaxel or docetaxel chemotherapy in high-risk breast cancer.** Int. J. Radiation Oncology Biol. Phys., 200; 48( 2) : 393–397. doi: 10.1016/s0360-3016(00)00636-2
22. 22. Burstein, H. J.; Bellon, J.R.; Galper, S.; Lu, H-M.; Kuter, I. ; Taghian, A.G.; Wong, J.; Gelman, R.; Bunnell, C.A.;Parker, L.M.; Garber, J.E.; Winer, E.P.; Harris, J.R.; Powell, S.N. **Prospective evaluation of concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for Stage II or III breast cancer.** Int J Radiat Oncol Biol Phys. 2006 ;64(2):496-504. doi: 10.1016/j.ijrobp.2005.07.975
23. Sanguineti,G.; Del Mastro, L.; Guenzi, M.; Ricci, P.; Cavallari, M.; Canavese, G.; Stevani, I. ; Venturini, M. **Impact of chemotherapy dose-density on radiotherapy dose-intensity after breast conserving surgery.** Ann Oncol. 2001; 12: 373-378. doi: 10.1023/a:1011125832331
24. Rouëssé, J. ; de la Lande, B.; Bertheault-Cvitkovic, F.; Serin, D.; Graïc, Y.; Combe, M.; Leduc B, V. V.; Demange, L.; Nguyen, T.D.; Castèra, D.; Krzisch.C.; Villet, R.; Mouret-Fourme, E.; Garbay, J.R.; Noguès, C.; Centre René Huguenin Breast Cancer Group. **A phase III randomized trial comparing adjuvant concomitant chemoradiotherapy versus standard adjuvant chemotherapy followed by radiotherapy in operable node-positive breast cancer: final results.** Int J Radiat Oncol Biol Phys.2006; 64(4):1072-80. doi: 10.1016/j.ijrobp.2005.10.011
25. Toledano,A.; Azria, D.; Garaud ,P.; Fourquet ,A.; Serin, D.; Bosset, J.F.; Miny-Buffet, J.; Favre, A.; Le Floch, O.;Calais, G. **Phase III Trial of Concurrent or Sequential Adjuvant Chemoradiotherapy After Conservative Surgery for Early-Stage Breast Cancer: Final Results of the ARCOSEIN Trial.** JCO 2007; 25(4):405-410. doi: 10.1200/JCO.2006.07.8576
26. Livi,L. ; Meattini, I.; Scotti,V.; Saieva, C.; Simontacchi, G.; Marrazzo, L.; Franzese, C.; Cassani, S.; Paiar, F.; Di Cataldo, V.; Nori ,J.; Sanchez, L.J.; Bianchi ,S.; Cataliotti, L.; Biti, G. **Concomitant adjuvant chemo-radiation therapy with anthracycline-based regimens in breast cancer: a single centre experience 2011.** Radiol Med. 2011 Oct;116(7):1050-8. doi: 10.1007/s11547-011-0652-2
27. Faul, C.A.; Brufsky, A.; Gerszten, K. ; Flickinger ,J.; Kunschner, A.; Jacob, H.;Vogel, V. **Concurrent sequencing of full-dose CMF chemotherapy and radiation therapy in early breast cancer has no effect on treatment delivery.** Eur J Cancer .2003; 39 : 763–768. doi: 10.1016/s0959-8049(02)00834-1
28. Fiets ,W.E.; van Helvoirt,R.P.; Nortier, J.R.; van der Tweel, I.; Struikmans ,H. **Acute toxicity of concurrent adjuvant radiotherapy and chemotherapy (CMF or AC) in breast cancer patients: a prospective, comparative, non-randomised study.** Eur J Cancer.2003;39:1081–1088.doi: 10.1016/s0959-8049(03)00178-3.
29. Arcangeli, G.;Pinnarò, P.; Rambone, R.; Giannarelli, D.; Benassi, M. **A phase III randomized study on the sequencing of radiotherapy and chemotherapy in the conservative management of early-stage breast cancer.** Int. J. Radiation Oncology Biol. Phys.2006; 64(1) : 161–167. doi:10.1016/j.ijrobp.2005.06.040
30. Han, S.; Kim, J.; Sohn,S.; Kwak ,G.H.; Kim, J.I.Y.; Park, K. **Feasibility of Concurrent Adjuvant Chemotherapy and Radiotherapy After Breast-Conserving Surgery in Early Breast Cancer.** J Surg Onc. 2007;95:45–50. doi: 10.1002/jso.20715.
31. Livi ,L. ; Saieva,C.; Borghesi , S.; Paoletti, L.; Meattini, I.; Rampini, A.; Petrucci, A.; Scoccianti, S.; Paiar,F.;Cataliotti, L.; Cataliotti , B.; Bianchi, S.; Biti, G.P. **Concurrent cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and radiotherapy for early breast carcinoma.** Int J Radiat Oncol Biol Phys. 2008 ;71(3):705-9.doi: 10.1016/j.ijrobp.2007.10.042.
32. Ismaili ,N.; Mellas, N.; Masbah ,O.; Elmajjaoui, S.; Arifi ,S.; Bekkouch ,I.; Ahid ,S.;Bazid, Z.; Tazi, M.A.; Erraki, A.; El Mesbahi, O.; Benjaafar ,N.; El Khalil, E.l.; Gueddari, B.; Ismaili ,M.; Afqir ,S.; Errihani, H. **Concurrent chemoradiotherapy in adjuvant treatment of breast cancer.** Radiat Oncol. 2009, 4:12- 15. doi:10.1186/1748-717X-4-12
33. Lu, Y.;Huang, H.; Yang, H.; Chen, D. **Randomized controlled trial of late-course concurrent versus sequential chemoradiotherapy after mastectomy and axillary surgery in locally advanced breast cancer.** Medicine . 2017; 96:41(e8252). doi 10.1097/MD.0000000000008252.
34. Hassan, A. A.; Ibrahim, N.Y.; Jassen, M.A.R. **Concurrent Paclitaxel and Radiotherapy for Node Positive Breast Cancer.** Gulf J Oncolog. 2019 ; 1(29):14-21. PMID: 30956192.
35. Woo, J.; Moon, B.I; Kwon ,H.; Lim, W. **Effect of radiotherapy sequence on long-term outcome in patients with node-positive breast cancer: a retrospective study.** Sci Rep.2022; 212:10729. doi:10.1038/s41598-022-14873-9.
36. Smith,B.D.; Bentzen ,S.M.; Correa, C.R.; Hahn, C.A.; Hardenbergh, P.H.; Ibbott, G.S.; McCormick, B.; McQueen, J.R.; Pierce, L.J.; Powell, S.N.; Recht, A.; Taghian ,A.G.; Vicini,F.A.; White, J.R.; Haffty, B.G. **Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline.** Int J Radiat Oncol Biol Phys. 2011;81:59-68. doi: 10.1016/j.ijrobp.2010.04.042.
37. Smith, B.D.; Bellon, J.R.; Blitzblau, R.; Freedman, G.; Haffty, B.; Hahn, C.; Halberg, F.; Hoffman, K.; Horst, K.; Moran, J.; Patton, C.; Perlmutter, J.; Warren, L. ; Whelan, T.; Wright, J.L.; Jagsi, R. **Radiation therapy**

**for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline.** Pract Radiat Oncol .2018; 8: 145-152. doi.org/10.1016/j.prro.2018.01.01

38. Whelan, T.J.; Pignol, J.P.; Levine, M.N.; Julian, J.A.; MacKenzie, R.; Parpia, S.; Shelley, W.; Grimard, L.; Bowen, J.; Lukka, H.; Perera, F.; Fyles, A.; Schneider, K.; Gulavita, S.; Freeman ,C. **Long-term results of hypofractionated radiation therapy for breast cancer.** N Engl J Med 2010; 362: 513–20. doi: 10.1056/NEJMoa0906260
39. START Trialists Group; Bentzen, S. M.; Agrawal, R. K.; Aird, E. G. A.; Barrett, J. M.; Barrett-Lee, P.J. J.; Bliss, M.; Brown, J.; Dewar, J. A.; Dobbs, H. J.; Haviland ,J. S.; Hoskin ,P.J.;Hopwood,P.; Lawton, P. A.; Magee, B. J.; Mills, J.; Morgan, D.A.L.; Owen, J. R.; Simmons, S.; Sumo,G.; Sydenham, M. A.; Venables, K.; Yarnold J.R. **The UK Standardisation of Breast Radiotherapy (START) trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.** Lancet Oncol 2008; 9: 331-41. doi: 10.1016/S1470-2045(08)70077-9.
40. START Trialists Group; Bentzen, S. M.; Agrawal, R. K.; Aird, E. G. A.; Barrett, J. M.; Barrett-Lee, P. J.; Bentzen, S.M.; Bliss , J. M.; Brown, J.; Dewar, J. A.; Dobbs, H. J.; Haviland, J .S.; Hoskin ,P. J.; Hopwood, P.; Lawton, P. A.; Magee, B. J.; Mills, J. ; Morgan, D.A.L.; Owen, J. R.; Simmons, S.; Sumo, G.; Sydenham, M. A.; Venables, K.; Yarnold, J. R. **The UK Standardisation of Breast Radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.** Lancet 2008; 371: 1098-107. doi: 10.1016/S0140-6736(08)60348-7
41. Deantonio, L.; Gambaro, G. ; Beldì, D. ; Masini, L. ; Sara Tunesi, S. ; Magnani, C. ; Krengli, M. **Hypofractionated radiotherapy after conservative surgery for breast cancer: analysis of acute and late toxicity.** Radiat Oncol. 2010; 5:112-119. doi: 10.1186/1748-717X-5-112
42. Hijal,T.; Al Hamad, A.A.;Niazi, T.; Sultanem, K.; Bahoric, B.; Vuong, T.; Muanza,T. **Hypofractionated radiotherapy and adjuvant chemotherapy do not increase radiation-induced dermatitis in breast cancer patients.** Curr Oncol 2010; 17(5) : 22-7. doi: 10.3747/co.v17i5.604
43. Kouloulias,V. ; Zygogianni,A .;Kypraiou, E. I.;Georgakopoulos,J.; Thrapsanioti, Z. ; Beli, I.; Mosa, E.;Psyrri A.;Antypas ,C.;Armbilia, C.;Tolia, M.;Platoni,K.;Papadimitriou ,C.;Arkadopoulos,N.; Genn atas, C.; Kyrgias, G.; Dilvoi, M.; Patatoucas, G.; Kelekis N.; Kouvaris, I. **Adjuvant chemotherapy and acute toxicity in hypofractionated radiotherapy for early breast cancer**. World J Clin Cases 2014 November 16; 2(11): 705-10. doi: 10.12998/wjcc.v2.i11.705
44. De Santic, M.C.; Bonfantini, F.; Di Salvp,F.; Dispinzeri, M.; Mantero, E.; Soncini,F.;Baili,P.; Sant,M.;Bianchi,G.;Maggi,C.; Di Cosimo, S.; Agresti,R.; Pignoli,E.;Valdagni,R.;Lozza,L. **Factors influencing acute and late toxicity in the era of adjuvant hypofractionated breast radiotherapy**. The Breast 2016; 29: 90- 5. doi: 10.1016/j.breast.2016.07.013.
45. Vijayaraghavan, N.; Vedasoundaram , P.; Mathew, J.M.; Menon, A.; Kannan, B. **Assessment of acute toxicities and early local recurrences in post mastectomy breast cancer patients by accelerated hypofractionated radiotherapy; a single arm clinical trial**. JBUON 2020; 25(5): 2265-70. PMID: 33277844
46. Van Hulle, H.; Naudts, D.; Deschepper, E.; Vakaet, V.; Paelinck, L.; Post, G.; Van Greveling , A.; Speleers, B.; Deseyne, P.; Lievens, Y.; De Neve ,W.; Veldeman, L.; Monten , C. **Accelerating adjuvant breast irradiation in women over 65 years: matched case analysis comparing a 5-fractions schedule with 15 fractions in early and locally advanced breast cancer**. J Geriatr Oncol. 2019;10:987–989. doi: 10.1016/j.jgo.2019.04.007.
47. Van Hulle, H.; Vakaet, V.; Bultijnck, R.; Deseyne, P.; Schoepen, M.; Van Greveling,A.; Post, G.; De Neve ,W.; Monten, C.;Lievens, Y.; Veldeman, L. **Health-related quality of life after accelerated breast irradiation in five fractions: a comparison with fifteen fractions.** Radiother Oncol 2020;151: 105e111 110 47e55. doi: 10.1016/j.radonc.2020.07.007.
48. Brunt,A.M.;Haviland,J.S.;Wheatley,D.A.;Sydenham, M.A.;Alhasso, A.;Bloomfield ,D.J.;Chan, C.;Churn, M .;Cleator, S.; Coles,C.E. ; Goodman, A.; Harnett, A.; Hopwood, P.; Kirby, A.M.; Kirwan, C.C.; Morris, C.; Nabi, Z.; Sawyer, E. N.; Somaiah, N.; Stones, L.; Syndikus, I.; Bliss, J.M.; Yarnold, J.R.; FAST-Forward Trial Management Group. **Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial.** Lancet 2020; 395: 1613-26. doi: 10.1016/S0140-6736(20)30932-6.
49. Isaac,N. ;Panzarella, T.; Lau, A.;Mayers ,C.; Kirkbride, P.;Tannock , I.F.; Vallis, K.A. **Concurrent Cyclophosphamide, Methotrexate, and 5-Fluorouracil Chemotherapy and Radiotherapy for Breast Carcinoma.** Cancer. 2002 ; 95(4): 696-703. doi: 10.1002/cncr.10744
50. Chen, W.C.; Kim, J.; Kim, E.; Silverman, P.; Overmoyer, B.; Cooper, B.W.; Anthony,S; Leeming, R.; Hanks, S.H.; Lyons, J.A. **A phase II study of radiotherapy and concurrent paclitaxel chemotherapy in breast-conserving treatment for node-positive breast cancer.** Int J Radiat Oncol Biol Phy. 2012 Jan 1;82(1):14-20. doi: 10.1016/j.ijrobp.2010.08.051
51. Wadasadawala ,T.; Anup, A.; Carlton, J.; Sarin, R.; Gupta, S.; Parmar ,V.; Pathak, R .; Ghosh, J.; Bajpai, J.; Gulia, S.; Krishnamurthy, . **CONcurrent ChEmotherapy and RadioTherapy in adjuvant treatment of**

**breast cancer (CONCERT): a phase 2 study.** Ecancermedicalscience. 2023; 17:1510. doi.org/10.3332/ecancer.2023.1510

52. Lazzari, G.; Benevento, I.; Montagna, A.; D'Andrea, B.; De Marco, G.; Castaldo, G.; Bianculli, A.; Tucciariello, R.; Metallo, V.; Solazzo, A.P. **Breast Cancer Adjuvant Radiotherapy in Up-front to Chemotherapy: Is there a worthwhile benefit? A preliminary report.** Breast Cancer: Targets and Therapy. 2024; :16 359–367. doi: 10.2147/BCTT.S471345
53. Yadav, B.S.;Gupta, S.; Dahiya, D.; Gupta, A.; Oinam , A.S. **Accelerated hypofractionated breast radiotherapy with simultaneous integrated boost: a feasibility study.** Radiat Oncol J. 2022 Jun;40(2):127-140. doi: 10.3857/roj.2021.01053.