Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Breast Cancer Adjuvant Radiotherapy in Up-Front to Chemotherapy: Is There a Worthwhile Benefit? A Preliminary Report

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Purpose: We administered a new breast cancer (BC) adjuvant therapy sequence that delivered postoperative radiotherapy (PORT) before chemotherapy (CT). Our aim was to assess the gain in time to start PORT and the G2–G3 acute–subacute toxicity rate of whole breast adjuvant hypofractionated radiotherapy (AH-RT) administered up-front to the third-generation adjuvant CT (A-CT) in high-risk nodal positive BC in a preliminary report at 2 years.

Methods: This retrospective study analysed the duration of treatment and safety of AH-RT administered up-front to A-CT in high-risk nodal positive BC patients (pts). Data on 45 pts treated between 2022–2023 were collected. All pts underwent the third-generation A-CT after AH-RT 15–5 fractions with or without a boost. Acute toxicity was scored according to CTCAE v5.0 for skin, pulmonary, and cardiac adverse events. Univariate and multivariate analyses were conducted to assess significant prognosticators for skin/lung/heart acute toxicities in the AH-RT 5–15 fractions arms and CT ($p < 0.005$).

Results: A reduction in the time to PORT initiation and overall adjuvant treatment time was recorded. RT was initiated 5 median weeks after surgery, and A-CT was performed 9 median weeks after surgery. The median duration of the entire adjuvant treatment was 35 weeks after surgery. At 6 months mean follow-up, no significant differences in G2–G3 toxicity were noted between the different hypofractionated RT arms, irrespective of the CT schedules, irradiated volumes, or boost (SIB or sequential) in univariate and multivariate analyses. In the multivariate analysis, no significant effects in CT schedules and AH-RT 5–15 arms for skin/lung acute toxicities ($p = 0.077$ and $p = 0.68$; 0.67 and 0.87, respectively) were recorded.

Conclusion: As a new PORT approach in BC, AH-RT up-front to the third-generation A-CT appeared safe with a low acute toxicity profile, providing an advantage in shortening the time from surgery to PORT initiation and the overall adjuvant treatment time.

Keywords: PORT, third-generation chemotherapy, hypofractionated radiotherapy

Introduction

Time to postoperative radiotherapy (PORT) or "killing time" is crucial in BC local control and survival.[1] As the first step in micro-metastatic migration, the tumour bed has been defined as a hub for the epithelial-to-mesenchymal transition (EMT) of tumour cells after surgery.[2,3] This process has been evocated as a physiological wound repair mechanism after lumpectomy, where residual immature tumour cells under the physiological signalings associated with inflammation due to the wound repair may acquire the capability to metastasize. Postoperative radiotherapy may act by eliminating these immature committed EMT tumor cells in the lumpectomy site or those that have taken EMT transition properties induced by wound repair in the microenvironment. Other effects of radiotherapy could result in an immunogenic systemic effect in preventing or reducing colonization after EMT tumor cells through an abscopal effect, which is a well-known effect induced by hypofractionated radiotherapy.[2]

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Thus, an early delivery of PORT to the tumour bed could induce an early anticancer response, as demonstrated in several models inspired by the IORT boost.[4] This study has clearly shown how the delivery of an IORT boost is able to modify the fluid profile from the irradiated wound by adding several anticancer immune properties and blocking the tumor cell growth. This is a rationale to deliver hypofractionated radiotherapy up front to adjuvant chemotherapy.

In recent years, adjuvant treatment for BC has improved owing to a better understanding of its biology and multidisciplinary team sharing decisions through breast unit teams worldwide. Customised systemic therapy and new radiation schedules have substantially changed the duration of adjuvant therapy, questioning the need for a new sequencing between local and systemic approaches.[5] Notably, the introduction of third-generation CT has prolonged the entire adjuvant systemic treatment span, whereas the duration time of RT with the adoption of new hypofractionated PORT schedules has substantially shortened.[6,7] Although the third-generation CT regimens have yielded a 20% reduction in BC mortality in comparison with previous regimens,[8] more than 12 weeks are necessary to complete the entire course, particularly when an unexpected acute toxicity occurs. This further delays PORT initiation.

PORT courses have been revolutionised worldwide with the introduction in clinical practice of new smart and easy fractionation schedules with 15 or 5 fractions (frs). Growing evidence from high-quality randomized clinical trials on moderately and accelerated hypofractionated whole- or partial-breast PORT has yielded many advantages over conventional whole-breast long-course RT.[9] Indeed, START,[10,11] Ontario,[12] Danish,[13] Postmastectomy,[14] FAST-Forward,[15] and YO-HAI5 trials[16] have clearly shown that long-term local control and survival are at least as effective as with 2 Gy daily fractions with similar or reduced normal tissue toxicity. Consequently, its routine use is considered time effective and advantageous in terms of quality of life, pt logistics, and substantial cost savings for healthcare systems.[17]

The current standard of care involves adjuvant CT, followed by adjuvant RT, since the Up-front–Outback trial results, which were published in 1996 and updated in 2005.[18,19] This trial showed no differences in toxicity, event-free status, distant metastases, or overall survival between the two sequencing arms. However, in this trial, CT consisted of the first-generation combination lasting at least 12 weeks, followed by standard RT of 2 Gy/fr delivered for at least 5 weeks. Notably, in the conclusions, the authors declared no certainty in replicating these results using longer CT regimens. Currently, hypofractionated PORT is reasonable to be considered up-front to systemic therapy because of the gain in time that can be spared from the entire treatment time. This gain could translate into a survival benefit overall. In this retrospective study, we aimed to evaluate whether a gain could be achieved in terms of adjuvant treatment time and the rate of G2–G3 acute and subacute toxicity outcomes using AH-RT up-front to long-course A-CT as a new PORT approach in a group of high-risk nodal positive BC patients (pts).

Methods

Study Population

This retrospective study was approved by our local institutional review board and ethical committee of the S. Carlo Hospital in Potenza (CEUR). This study complies with the Declaration of Helsinki. Informed consent was obtained from all the treated pts. Data from 45 pts treated with surgery and adjuvant therapy in 2022–2023 were collected and analysed. Pts who received neoadjuvant CT were excluded. All pts had nodal positive BC. Breast conserving surgery (BCS) was performed in 30 pts and mastectomy in 15 pts. Eight pts had close or positive margins that were unsuitable for re-excision. The mean age of pts was 65 years (45–80). (Table 1)

Up-Front Hypofractionated Radiotherapy

Hypofractionated PORT was delivered to all pts on the breast or chest wall (CW), with nodal areas consisting of the supraclavicular (SVC) ± internal mammary chain (IMC). IMRT and VMAT were performed. Sequential or simultaneous integrated boost (SIB) was allowed in premenopausal women under 60 years of age and in cases with close margins or R1 not suitable for re-excision. Hypofractionated PORT was performed on the residual breast, CW, and nodal areas as follows.

Table 1 Patients and Treatment Findings (Surgery and RT Volumes)

Patients 45 (pts) Mean age 65 yrs (45–80)	RT 15 frs/ 40.05 Gy 28 pts	RT 5 frs/28.5 Gy 17 pts
BCS	22	12
MASTECTOMY	6	5
IMC- RT	11 (CW 6)	8 (CW 5)
SIB	20 (3.2 Gy/fr)	6 (6.4 Gy/fr)
SEQ BOOST	14 (4 CW)	–
R1 /CLOSE MARGIN	5	3

Abbreviations: frs, fractions; BCS, Breast Conserving Surgery; IMC, Internal Mammary Chain; CW, Chest wall; SIB, Simultaneous integrated boost; R1= microscopic infiltrated margin.

AH-RT - 5 frs was delivered to 17 pts. SVC was treated in all pts; IMC was added in eight pts; and the CW in five pts with an unreconstructed CW was treated. A boost was delivered via SIB according to age and R1 margin status in six pts. AH-RT – 5 frs on alternate days was 5.7 Gy/fr/28.5 Gy (SIB 6.4 Gy/fr/32 Gy) and 5.4 Gy/fr/27 Gy on nodal areas.

AH-RT - 15 frs was administered to 28 pts, and the CW in 10 pts was treated. The SVC area with the IMC was irradiated in 11 pts; in the remaining pts, only the SVC area was included. The boost was delivered in 30 pts, with SIB to 20 pts. AH-RT-15 consisted of 2.67 Gy/fr/40.05 Gy; sequential boost was 2.5 Gy/fr/10 Gy and administered to 14 pts (10 n +4 CW). SIB was 3.2 Gy/fr/48 Gy (Table 1).

Out-Back Third-Generation Chemotherapy

All pts underwent the third-generation A-CT by medical oncologists based on age, comorbidities, oncotype test results, molecular phenotypes, and nodal involvement. A-CT was started after 10 mean days (8–15 days) off RT and after eight median weeks from surgery (6–12 weeks). In HER2-positive N+ pts, A-CT schedules with 4–12 cycles of anthracycline–taxane–anti-HER2 combination (AC 4 + 12 weeks paclitaxel + trastuzumab) and paclitaxel 12 weeks + trastuzumab followed by trastuzumab were provided. For HER2-negative N+ pts, A-CT with EC 8 cycles, AC 4 + docetaxel 4, dose-dense AC followed by 12 weeks of paclitaxel were prescribed as per the guidelines, as presented in Table 2.

Table 2 Patient Characteristics According pN Status and Third-Generation Adjuvant Chemotherapy

A-CT	pN1	pN2	pN3
45 pts	20	15	10
Ac 4 + 12 Tx + Tsz	3	3	4
PTx + Tsz	4	5	3
EC 8	3	2	2
Ac 4 + Docetax 4	2	2	3
Dd AC+ Tx	2	4	4

Abbreviations: Ac, anthracyclines; Tx, Taxol; Tsz, Trastuzumab; PTx, Paclitaxel; EC, Epirubicin - Ciclofosfamide; Docetax, docetaxel; Dd, dose dense.

Toxicity Assessment and Follow-Up

Acute toxicities were recorded by treating physicians one week off RT and every CT cycle and scored according to CTCAE v5.0 for skin, pulmonary, and cardiac adverse events. Follow-up was conducted after 2 weeks off RT, 1 month, and 3–6–9–12 months during the first year. Subsequent follow-ups were conducted yearly.

Study Endpoints

The primary endpoint of this study was the evaluation of the gain in time to RT from surgery and the overall adjuvant scheduled therapy duration from the date of surgery. The secondary endpoint was to assess the rate of acute G2–G3 toxicity using CTCAE v5.0 for the skin, lung, and heart,[20] considering the time from the end date of RT to the date of the first recorded toxicity.

Statistical Analysis

Univariate analysis with paired *t*-tests was used to evaluate the correlation between G2–G3 skin, lung, and heart toxicity and sequential CT with new drug combinations as taxanes for the two hypofractionated RT schedules (AH-RT 5–15 frs). Pearson covariance was used for multivariate analysis. Cox proportional hazards regression was used to define the cumulative incidence of G2–G3 skin and lung toxicities in the two hypo-RT arms. For statistical analyses, SPSS (version 21.0; IBM Corp., Armonk, NY, USA) was used, and statistical significance was set at $p < 0.05$.

Results

Patients and Treatment Time

Pts, tumour characteristics, surgery, and treatment data are presented in Tables 1 and 2. AH-RT was started 35 median days (5 weeks) after surgery (30–45 days). A-CT was performed after 10 median days (8–15 days) off RT, corresponding to 9 median weeks (6–13 weeks) from the surgery. The median duration of the entire adjuvant treatment was 35 weeks from the surgery (26–40 weeks), according to the RT and CT schedules chosen per pt (Table 3).

G2–G3 Radiation Induced Toxicity

At 6 months mean follow-up (3–12 m), acute G2 skin toxicity was experienced in 10/45 pts (22%) and G3 in 2/45 (4%) pts. G3 skin toxicity was observed in one pt after the first cycle of EC; she had received SIB −5 frs for pT4 R1 status treated with a bolus. The other pt was treated with a paclitaxel schedule after SIB 15 frs. The incidence of pneumonitis G2 was 2%; it occurred in one pt treated with AC-taxane after RT 15 frs on ICM and no boost. The incidence of pneumonitis G3 was 2%; it was recorded in one pt treated with EC after SIB 5 frs on CW (Table 4). No cardiac toxicity was observed.

Treatment Outcomes

Univariate analysis revealed no differences in G2–G3 acute skin and lung toxicities between the two AH-RT arms and CT with or without taxane combinations. Consequently, no statistical differences were noted in the AH-RT - 5 frs with taxanes (P = 0.52, OR 0.65 [CI 0.21–2.30]) or without taxanes (P = 0.58, OR 1.47 [CI 0.44–4.89]) and in the AH-RT - 15 frs with taxanes (P = 0.60, OR 0.75 [CI 0.28–2.50]) or without taxanes (P = 0.56, OR 1.57 [CI 0.54–4.98]), as reported in Table 5.

Table 3 Comparison of Gain in Timing Weeks (Ws) to Radiotherapy from Surgery Between the Reference Trial and Our Retrospective Study

Weeks mean	Upfront -Outback /Trial	Our Study
Time to RT from surgery	RT- f 5 ws CT-f 31 ws	RT 5 ws
Time to CT from surgery	RT -f 29 ws CT-f 13 ws	CT 16 ws

Abbreviation: ws, weeks.

Table 4 G2-G3 Acute-Subacute Radiation Induced Toxicity

TOXICITY pts (%)	AH-RT 5	AH-RT 15
G2 -SKIN 10 (22)	3	7
G3 " 2 (4)	1	1
G2 -LUNG 1 (2)	–	1
G3 " (2)	1	–

Abbreviations: AH-RT 5, hypofractionated radiotherapy 5 fractions; AH-RT 15, hupofractionated radiotherapy 15 fractions.

Table 5 Univariate Analysis *t*-Test for Acute Toxicity for Skin and Lung

Toxicity	AH-5 fr	AH-15 fr
Skin Tax	(P=0.52, OR 0.65 [CI 0.21–2.30])	(P=0.60, OR 0.75 [CI 0.28–2.50])
« No Tax	(P=0.58, OR 1.47 [CI 0.44–4.89])	(P=0.56, OR 1.57 [CI 0.54–4.98])
Lung Tax	(P=0.70, OR 0.85 [CI 0.28–2.56])	(P=0.76, OR 1.62 [CI 0.58–4.88])
« No Tax	(P=0.68, OR 0.97 [CI 0.48–5.19])	(P=0.59, OR 1.67 [CI 0.64–4.55])

Abbreviations: Tax, Taxanes; No Tax, no Taxanes.

Multivariate analysis confirmed no significant effect in CT schedules and AH-RT 5–15 arms for G2–G3 skin/lung acute toxicities (p = 0.077 and p = 0.68; 0.67 and 0.87, respectively). Furthermore, for IMC irradiation (p = 0.065; 0.88) and SIB (p = 0.89; 0.99), no significant differences were observed, respectively, for the two arms, as presented in Table 6. At 6 months, the cumulative incidence of G3 skin toxicity was 3% and 2.5% for AH-RT - 5 frs and AH-RT - 15 frs (p = 0.672), respectively, and lung toxicity was 3.2% and 2.5% (p = 0.618), respectively (Figure 1).

Table 6 Multivariate Pearsons Covariance

		Tox- S	AHRT-15 fr	AHRT-5 fr	SIB	ICM- RT	Tox- L	AC-T
AH-RT-15 fr	R	0.255(**)	1	0.130(**)	0.127	0.485(**)	0.485(**)	−0.073
	Sig.	> 005		0.077	0.067	> 005	0.000	0.289
AH-RT-5 fr	R	0.403(**)	0.430(**)	1	0.285(**)	0.938(**)	0.969(**)	0.022
	Sig.	> 005	0.089	0.678	0.00097	> 005	0.0065	0.750
SIB	R	0.110	0.127	0.285(**)	1	0.285(**)	0.256(**)	−0.019
	Sig.	0.111	0.067	0.000		<0.001	0.000	0.788
AC-Antra	R	0.455(**)	0.485(**)	0.969(**)	0.256(**)	0.938(**)	1	0.048
	Sig.	> 005	0.056	0.007	0.000	> 005	0.045	0.490
AC-T	R	−0.085	−0.073	0.022	−0.019	0.022	0.048	1
	Sig.	0.221	0.289	0.750	0.788	0.750	0.490	

Notes: **Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: Tox, toxicity; S, skin; L, lung; Antra, Antracyclines, AC-T, Taxanes; ICM-RT, internal mammary chain; SIB, simultaneous integrated boost; AHRT, Adjuvant Hypofractionated Radiotherapy.

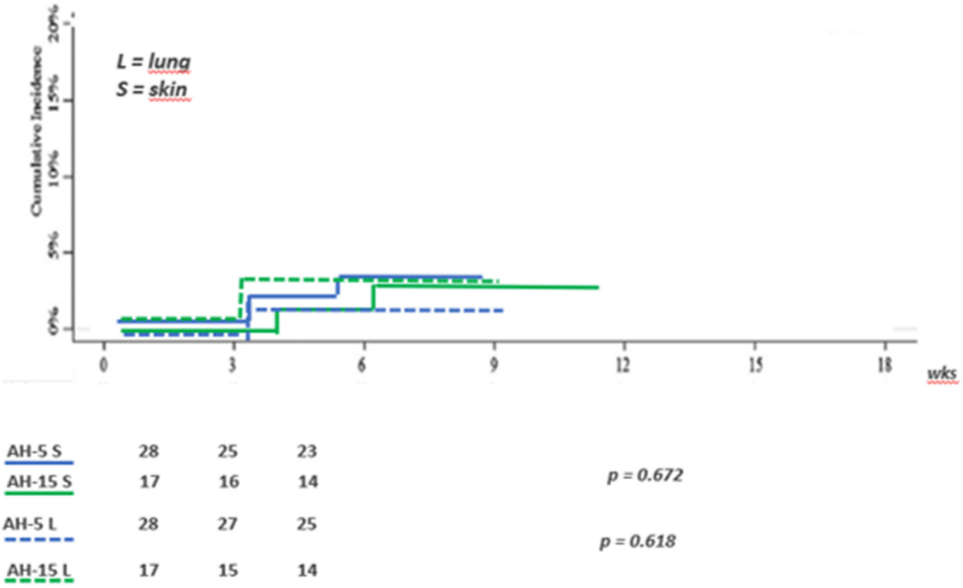

Figure 1 Six months cumulative incidence of G3 skin (S) toxicity = 3% and 2.5% for AH-RT - 5 and AH-RT - 15 fr (p = 0.672); lung (L) toxicity was 3.2% and 2.5% (p= 0.618).

Discussion

Adjuvant treatment with local RT and systemic CT is a milestone in the treatment of high-risk BC. Adjuvant CT reduces the risk of distant recurrence, whereas adjuvant RT ensures local control. However, through this action, RT has a survival benefit for BC pts, as recently demonstrated by a comprehensive analysis of the complete DBCG 82bc.[21] To explain this effect, in a rebuttal review, Formenti S and Demaria C defined the tumour bed as a site for epithelial to mesenchymal transition (EMT) of tumour cells after surgery as the first step for micro-metastatic migration from the surgical bed.[2,3] Thus, optimising the timing of PORT may be a reasonable way to minimise this risk. Based on this background and in response to our previous concern,[5] we treated 45 high-risk, nodal positive BC pts with PORT before adjuvant CT.

Currently, A-CT has preceded A-RT since the results of the Up-front–Out back trial, a milestone trial published in 1996 and then updated in 2005.[18,19] However, the introduction of the third-generation systemic therapy and hypofractionated RT has raised the issue of whether new sequencing approaches could yield some advantages. The first issue to verify is whether PORT administered up-front to CT really achieves a gain in the gap time between surgery and the start of RT, which affects the overall adjuvant treatment time. As well acknowledged, time factor is crucial for the radiation-induced benefit on local control.[22] Indeed, published studies have demonstrated that RT initiated more than 12 weeks after surgery may affect survival outcomes, as recently shown in an Ontario population-based study. In this study, a delay in RT over 12 weeks from surgery or 6 weeks from the end of CT had a negative effect on the survival probability.[23]

In the reference trial, 244 pts were randomised to receive CT before RT versus RT before CT. Chemotherapy consisted of 12 weeks of therapy with four CAMPF. RT was delivered in 25–30 frs using standard fractionation. In the first report by Recht in 1996, 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. An interval of more than 16 weeks was observed 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. In the present retrospective study, we recorded a reduced gap time from surgery to the start of the entire adjuvant treatment that was nearly five weeks for the entire group. The time to start CT was less than 16 weeks from surgery.[18]

The second issue to assess is whether this approach is safe with regard to skin, lung, and heart acute–subacute toxicities when considering nodal or chest irradiation before CT. In the reference trial, in the group treated with nodal RT, the incidence of skin toxicity was 15% in the RT-first group (17/115) and 11% in the CT-first group (12/112); p = 0.43. The incidence of radiation pneumonitis was 9% (4/44) in the RT-first group and 0% (0/77) in the CT-first group (0/42); p = 0.12.[18] However,

these data are not comparable with the present study results because of the different RT fractionations and CT combinations. Since the introduction of hypofractionated RT worldwide, many concerns have been raised regarding the side effects in pts undergoing hypofractionated RT following adjuvant CT. The new recommendations of the ASTRO consensus guidelines in 2018 strongly addressed this issue by considering the safety of this combination.[24] In real life studies using the conventional sequencing of modern A-CT followed by AH-RT, a rate of G2–G3 acute skin toxicities ranging from 5% to 27% has been reported.[25–27] Previously, according to the study by Hijal T et al on 162 pts treated with hypofractionated RT with (48%) or without adjuvant CT regimens with anthracyclines and taxanes, in the group treated with CT, the incidence of G3 acute skin toxicity was 2.1% whereas that of G1–2 toxicity was 62.5%.[28] Thereafter, in a retrospective study, Kouloulias et al reported a 7.8% rate of G2 acute skin toxicity and 2.6% of G3 toxicity. In addition, no significant correlation was noted between toxicity grading and CT in multivariate analysis.[29] Furthermore, in a prospective study conducted by De Sanctis et al on 510 pts treated with three CT anthracycline-taxane cycles followed by three CMF-containing cycles with sequential hypofractionated RT with or without boost according to Ontario or UK-START trials, data on acute toxicity were similar. The mean time between CT and RT was approximately 2 months (6 days–3.8 months). More than 20% of pts developed G2 or G3 acute skin toxicity, and 99.6% of them had no late skin toxicity. In multivariate analysis, CT was not significantly associated with toxicity ($p = 0.26$).[30] Data obtained from conventional sequencing studies are consistent with the results of our approach. The effects of nodal or CW irradiation on the toxicity should also be evaluated. According to the data from the HYPOBREAST prospective study, in a cohort of pts treated with hypofractionated RT on nodal areas after adjuvant CT, grade 2 or higher dermatitis was reported in 10.7% pts.[31] Moreover, in a study by Vijayaraghavan et al conducted on 67 pts almost treated with anthracyclines plus taxanes followed by hypofractionated postmastectomy RT with VMAT or IMRT, grade 2 and higher acute radiation dermatitis was reported in 11.9% pts. Only one pt developed a grade 3 skin reaction.[32] In the present study, nodal and CW irradiation showed no significant toxicities, irrespective of the hypofractionation arm and CT combination. Acute lung toxicity is another issue because symptomatic radiation pneumonitis has been reported with an incidence ranging from 0–7% depending on post-mastectomy RT, lung dosimetry, and RT modalities (VMAT, IMRT versus 3D techniques).[33,34] Herein, this rate was similar to that obtained using conventional sequencing. In an interim report by Jamora K et al on hypofractionated 3D postmastectomy RT in pts adjuvantly treated with anthracycline plus taxane-based regimens, the incidence of G2 skin toxicity was 68% and that of G3 skin toxicity was 63%, and any grade pneumonitis was observed.[34] In a study by Vijayaraghavan, the incidence of grade 2 and higher acute pneumonitis was 7.5%.[32] Cardiac toxicity was not recorded, probably because of the fulfilment of the constraints of the unexposed heart to upfront anthracycline regimens.[35] In summary, based on these comparisons, the use of AH-RT 5–15 frs before the adjuvant third-generation CT, as in our study, provided two encouraging answers in response to the question in the headline. First, this approach was advantageous because it reduced the time from surgery to radiation initiation. This effect could translate into improved local and distant controls. This hypothesis was supported by data from Belletti et al on the effect of IORT boost in blocking the proliferation and migration of cancer cells from the tumour bed, which is considered a hub for EMT migration.[4] In this study, authors clearly demonstrated the effect of IORT boost in enhancing the anti-inflammatory and the anticancer immunoresponse by fluid from the irradiated wounds. This effect was not found in the fluid taken from unirradiated patients, suggesting that an immune killing action is provided. Moreover, an "abscopal effect" induced by hypofractionated radiotherapy could be evocated adding a benefit on occult distant metastases.[2] This new sequencing opens up new scenarios in light of novelties with adjuvant immunochemotherapy as shown by KEYNOTE trials in early and advanced triple negative breast cancer (TNBC).[36,37] It is reasonable to hypothesize a beneficial effect by the combination of up-front adjuvant radiotherapy to immune-chemotherapy in PD-L1 negative TNBC.[38] Another advantage to consider is the reduction of the overall adjuvant treatment time span. This parameter may impact favourably not only on health costs as already recorded by the introduction of hypofractionated radiotherapy in the clinical practice[17] but on patients logistics and health-related quality of life as reported by several cost–benefit analyses.[39]

Second, this new approach appeared to be safe, without substantial differences from the conventional sequence in terms of acute–subacute toxicities. This study has several limitations because it was a retrospective analysis conducted on a few pts treated with up-front hypofractionated RT and had a short follow-up time. However, this finding suggested that administering AH-RT before long-course A-CT was safe and cost-effective for the overall adjuvant therapy treatment time.

Conclusions

This first report is an interim analysis assessing the acute and subacute toxicity outcomes of adjuvant hypofractionated RT up-front to the adjuvant long-course third-generation CT and the benefit of early delivery of PORT after surgery. Data on survival outcomes will be provided next after a longer follow-up period. Further studies with larger pts cohorts are necessary to validate the rationale of this new sequencing,[5] that respects the principle that delays in RT should be as short as reasonably achievable (ASARA), as declared by Mackillop WJ in 1996,[40] although others concluded that starting RT as soon as possible after BCS may not be necessary.[41] Thus, timing sequencing still remains an unsolved issue, but a new sequencing as described in our experience opens up new therapeutic scenarios.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that may have influenced the work reported in this study.

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