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Safety of pre- or postoperative accelerated radiotherapy in 5 fractions: A randomized pilot trial

Vakaet Vincent, MD [a, b], Van Hulle Hans, PhD [a, *], Van de Vijver Koen [c, d], Hilderson Ingeborg [e], Naert Eline [e, f], De Neve Wilfried [a], Vandorpe Jo [c, d], Hendrix An [a], Göker Menekse [g], Depypere Herman [a, g], Vergauwen Glenn [g], Van den Broecke Rudy [a, g], De Visschere Pieter [d, h], Braems Geert [a, g], Vandecasteele Katrien [a, b], Denys Hannelore [e, f], Veldeman Liv [a, b]

[a] Dept. of Human Structure and Repair, Ghent University, Belgium
[b] Dept. of Radiation Oncology, Ghent University Hospital, Belgium
[c] Dept. of Pathology, Ghent University Hospital, Belgium
[d] Dept. of Diagnostic Sciences, Ghent University, Belgium
[e] Dept. of Medical Oncology, Ghent University Hospital, Belgium
[f] Dept. of Internal Medicine and Pediatrics, Ghent University, Belgium
[g] Dept. of Gynaecology, Ghent University Hospital, Belgium
[h] Dept. of Radiology and Nuclear Medicine, Ghent University Hospital, Belgium

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ABSTRACT

Objective: Neo-adjuvant radiotherapy (NART) for breast cancer has shown promising survival results in retrospective trials. However, there are some obstacles such as a chemotherapy delay, an increased overall treatment time (OTT) and the risk of increasing surgical morbidity. Accelerated radiotherapy (RT) in 5 fractions allows to deliver NART in a very short time span and minimizes the delay of surgery and chemotherapy. This trial investigates this NART schedule for safety, feasibility and OTT.

Material and methods: Twenty patients eligible for neo-adjuvant chemotherapy (NACT) and breast conserving surgery, were randomized between NART before NACT or NACT and postoperative RT. In both arms, RT treatment was given in 5 fractions to the whole breast with a simultaneously integrated boost (SIB) on the tumor(bed). Lymph node irradiation was given concomitantly in case of lymph node involvement. OTT was defined as the time from diagnosis to last surgery in the intervention group, while in the control group the time between diagnosis and last RT-fraction was used. In the intervention group NACT-delay was defined as time between diagnosis and start of chemotherapy.

Results: 20 patients were included, and 19 patients completed treatment. OTT was significantly shorter in the intervention group (mean 218 days, range 196–253) compared to the control group (mean 237, range 211–268, $p = 0.001$). The difference in mean duration from diagnosis to the first treatment was a non-significant 4 days longer (31 vs 27 days, $p = 0.28$), but the start of NACT after diagnosis was delayed by 21 days (48 vs 27 days, $p < 0.001$). NART did not result in additional surgery complications.

Conclusion: This pilot trial is the first to report on accelerated NART in 5 fractions with SIB. NART before NACT resulted in a shorter OTT with good safety results.

* Corresponding author. University Hospital Ghent, Department of Radiotherapy, Entrance 98 Corneel Heymanslaan, 10 9000, Ghent, Belgium.
E-mail addresses: vincent.vakaet@ugent.be (V. Vincent), hans.vanhulle@ugent.be (V.H. Hans), koen.vandevijver@ugent.be (V.V. Koen), ingeborg.hilderson@uzgent.be (H. Ingeborg), eline.naert@uzgent.be (N. Eline), wilfried.deneve@ugent.be (D.N. Wilfried), jo.vandorpe@ugent.be (V. Jo), an.hendrix@ugent.be (H. An), menekse.goker@uzgent.be (G. Menekse), herman.depypere@ugent.be (D. Herman), glenn.vergauwen@uzgent.be (V. Glenn), rudy.vandenbroecke@ugent.be (V.B. Rudy), pieter.devisschere@ugent.be (D.V. Pieter), geert.braems@ugent.be (B. Geert), katrien.vandecasteele@ugent.be (V. Katrien), hannelore.denys@ugent.be (D. Hannelore), liv.veldeman@ugent.be (V. Liv).

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1. Introduction

Neo-adjuvant chemotherapy (NACT) has recently become the standard of care for selected high-risk early breast cancer patients, not only for tumor downstaging, but also for response monitoring [1]. In case of residual disease after NACT, better oncological outcomes are observed with treatment escalation, in Her2-positive and triple negative breast cancer (TNBC) [2,3]. NACT also leads to a higher rate of breast conserving surgery (BCS), but at the risk of higher local recurrence in older studies (inclusion from 1983 to 2002) [4]. Historically, the role of tumor downstaging to increase the rate of BCS was reserved for neo-adjuvant radiotherapy (NART), showing satisfactory cosmetic results and low complication rates [5–9]. In contrast, potential disadvantages of NART are a delay of NACT, an increase in the overall treatment time (OTT), and a higher risk of surgical morbidity. Recent advances in breast cancer radiotherapy (RT) could provide a solution. Accelerated RT in 5 fractions did not increase the risk of local relapse at 10 and 5-years in the recently published FAST and FAST-FORWARD trials, respectively [10,11]. Moreover, acceleration in 5 fractions resulted in lower acute toxicity with similar late toxicity, better health related quality of life (HRQoL), and OTT [10,12–14]. The European Society of Medical Oncology (ESMO) guidelines recommend a radiotherapy boost to the tumorbed in patients with a high risk of recurrence [1], as is often the case in patients receiving NACT. In the FAST-FORWARD trial, the boost was given in additional fractions after whole breast radiotherapy, adding at least one week to the treatment [10]. A further decrease in OTT can be achieved by a simultaneously integrated boost (SIB) to the tumor(bed) in the treatment without decreasing cosmesis or increasing acute and late toxicity [15–17]. Using NART in 5 fractions with SIB should result in even a shorter OTT, since the waiting time between surgery and RT is omitted. Treatment delays, not only between symptoms and diagnosis, but also between diagnosis and surgery or start of NACT, have been associated with worse survival for aggressive tumors like TNBC, although the causality remains questionable [18–27]. Consequently, changing treatment sequences should not result in a delay between diagnosis and the surgery or the first treatment. To confirm the theoretically shorter OTT and acceptable toxicity after NART, the pre- or post-operative accelerated radiotherapy (POP-ART) randomized pilot trial was undertaken. To our knowledge, this is the first study investigating radiotherapy in 5 fractions in the neo-adjuvant setting. This report details the differences in treatment durations between both groups, in addition to differences in surgery complications, mastectomy rate, radiotherapy toxicity and response rate.

2. Materials and methods

2.1. Patients

The full protocol of the POP-ART trial has previously been published [28]. Twenty female breast cancer patients (≥18 years of age) eligible for NACT according to multidisciplinary decision, were randomized between NART followed by NACT and surgery (intervention group) or NACT followed by surgery and postoperative RT (control group). All patients were treated at Ghent University Hospital. Potential reasons for proposing NACT to patients included triple negative or Her2-positive biology or downsizing of large tumors. A written informed consent was obtained from all patients before enrollment in the trial. Exclusion criteria were distant metastasis, inflammatory breast cancer, multifocal tumor lesions, lobular carcinoma, a history of breast cancer, chemotherapy, RT, or reconstructive breast surgery, planned mastectomy and patients unfit for NACT treatment.

2.2. Trial design

The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol was approved by the local ethics commission and registered at clinicaltrials.gov (NCT03783364). Fig. 1 shows an overview of the treatment sequence in both arms with the predicted duration for each part. In the intervention arm the port-a-cath placement was completed within 7 days after the ending of NART, followed by NACT shortly afterwards. According to the protocol, the time was equal for NACT and recovery between both treatment arms.

2.3. Treatment procedures

All patients received extensive imaging before any treatment including ultrasound-guided tissue biopsy and marking of the tumor using a clip, magnetic resonance imaging (MRI) of the breast, and either fine needle aspiration cytology (FNAC) in case of a suspicious lymph node or sentinel node biopsy (SNB) if no lymph node involvement was seen during imaging.

The chemotherapy and surgical protocols were the same in both treatment arms. NACT consisted of 4 cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 or 3 weeks, followed by 12 weekly cycles of paclitaxel with or without carboplatinum. In case of Her2 amplified tumors, lymph node negative patients received trastuzumab every 3 weeks, concomitantly with paclitaxel, whereas lymph node positive patients received treatment with a combination of trastuzumab and pertuzumab. Chemotherapy adaptation based on treatment toxicity or tumor response was allowed, to allow best current practice.

RT was given in 5 fractions up to a total dose of 28.5Gy (5.7Gy per fraction) to the whole affected breast with a SIB up to 31 Gy (6.2Gy per fraction) on the tumor(bed). In case of pathologically confirmed lymph node involvement (either on SNB or FNAC), the level I-IV axillary lymph nodes were irradiated to 27 Gy (5.4 Gy per fraction). RT was delivered over 10–12 days with at least one day interval between fractions. In the intervention arm the SIB was delineated using the gross tumor volume (GTV) based on MRI and expanded by a 5 mm clinical target volume (CTV) margin and a 5 mm planning target volume (PTV) margin. Around this PTV, a dose fall-off region of 1.5 cm was created receiving a minimum dose of 27.08 Gy with 95% receiving at least 27.9 Gy. In the control arm, the SIB was delineated using a CTV based on the surgical clips, histology report and all available pre-operative information. A dose fall-off region of 2 cm around this CTV was defined, receiving a minimum dose of 27.08 Gy with 95% receiving at least 27.9 Gy. The axillary lymph node regions were delineated using the PROCAB guidelines [29]. Level I was included at the discretion of the treating physician. Breast-only RT was delivered in prone position, breast + nodal RT was delivered in supine position.

BCS was always attempted, unless genetic testing during treatment demonstrated a high genomic risk for breast cancer. In this case, bilateral mastectomy was performed. In case of pathologically confirmed lymph node involvement (either on FNAC or SNB), an axillary dissection was performed.

2.4. Endpoints

The primary endpoints of the trial are: 1) safety, 2) feasibility, and 3) overall treatment time (OTT). Secondary endpoints include tumor response, therapy compliance, and treatment complications.

OTT was measured from the first pathologic confirmation of the diagnosis until the last day of RT in the control arm, or the day of the last surgery in the intervention arm. Tumor response to neo-

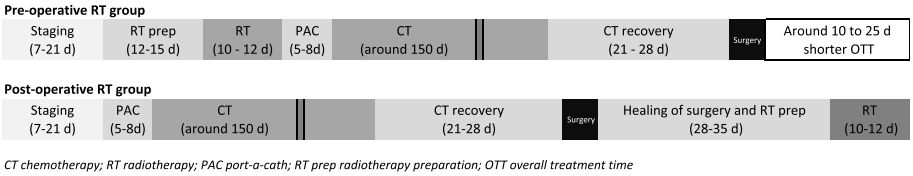

Fig. 1. Schematic overview of the time schedule in both treatment arms.

adjuvant treatment was evaluated using the pathological complete response (pCR) rate. The rate of patients finishing all 4 EC cycles and 12 paclitaxel cycles was measured. Patients were followed until 6 months after surgery (intervention arm) or RT (control arm) to determine any treatment complications or any additional surgeries including mastectomy. Acute RT toxicity was determined two to four weeks after the last fraction, using standardized questionnaires previously published [12].

2.5. Statistical analysis

All analyses were done on an intention-to-treat (ITT) basis. The study was powered to detect a 14-day difference in OTT between both groups, with 80% percent power at an alpha level of 0.05 using a two-sided Student's t-test. The proportion of patients requiring mastectomy, with surgical complications or achieving a pCR was compared using a 2-sided Fisher's Exact test (to account for small numbers).

3. Results

Of the 20 patients randomized, 19 patients were analyzed in the OTT analysis. One patient (without lymph node involvement) in the control group was excluded from analysis since she did not receive RT due to progression during NACT (a “rescue” mastectomy was performed). Table 1 shows the baseline characteristics in both groups. One patient randomized to NART crossed over to the NACT arm due to uncertainty about lymph node involvement during staging.

Table 2 gives an overview of the duration in days from diagnostic biopsy to the start of the first treatment, start of NACT, surgery and the end of treatment. OTT was significantly shorter in the intervention group (mean 218 days, range 196–253) compared to the control group (mean 232, range 211–268, $p = 0.03$). The difference in mean duration from diagnosis to the first treatment was a non-significant 4 days longer (31 vs 27 days, $p = 0.28$) in the intervention group. The start of NACT after diagnosis was delayed by on average 21 days in the intervention arm (48 vs 27 days, $p < 0.001$).

An overview of pCR, chemotherapy, surgery and RT details is found in Table 3. The proportion of patients with a pCR was similar between both groups (6/10 vs 6/9, $p = 1.0$). NART did not result in a lower percentage of patients finishing the complete NACT treatment (7/10 vs 4/9, $p = 0.37$). All patients had good wound healing.

4. Discussion

The POP-ART trial is a pilot trial demonstrating NART in 5 fractions before NACT is feasible and does not lead to a longer OTT. On the contrary, due to eliminating the waiting time between surgery and the start of RT, the resulting OTT is on average 14 days shorter. Compared to other studies, a relatively short OTT in both treatment arms was achieved by using a RT schedule in 5 fractions, delivered over 10–12 days. The RT schedule in 5 fractions is still experimental, although the results from the YO-HAI5, FAST and FAST-FORWARD trials are promising [10–12]. The UK FAST trial (5 fractions over 5 weeks) and FAST-FORWARD trial (5 fractions over 5 days) showed, compared to 25 or 15 fractions, no significant differences in relapse rates or survival as expected based on radiobiology, nor an increase in normal tissue toxicity after 10 years and 5 years, respectively [10,11]. However, less than 4% of patients included in the FAST and FAST-FORWARD trials received NACT. For the 5-fractions schedule over 10–12 days no long-term randomized evidence exists. An interim analysis of the YO-HAI5 study, randomizing between 5 fractions over 10–12 days and 15 fractions over 3 weeks, showed less acute toxicity [12] and better short-term HRQoL for the 5 fractions schedule [14]. A matched-case analysis with patients treated in 15 fractions, showed less 2-year toxicity except for fibrosis outside of the tumour bed [30].

Generally, the beginning of the cancer treatment was not delayed (31 vs 27 days), but the start of NACT was delayed by around 20 days due to RT preparation and delivery. If NACT were to be given first, some of the advantages of NART, like better targeting of the high dose region or the induction of an immune response, might get lost. A solution is giving chemotherapy and radiotherapy concomitantly, which has been done in several trials in the adjuvant setting [8,31–35]. However, the combination of accelerated RT in 5 fractions with concomitant chemotherapy has never been tested before and might lead to an increase in toxicity. The only randomized trial including 716 patients, comparing concomitant and sequential radio- and chemotherapy after surgery, resulted in no advantage of adjuvant concomitant chemo-radiotherapy for disease free survival or overall survival, but an increase in grade 2 or greater late side effects [36,37]. However, the node-positive subgroup did seem to have a significantly better locoregional control after concomitant chemo-radiotherapy.

NART has historically been used for downstaging to increase the rate of BCS, especially in locally advanced breast cancer [5–8,34,38–41]. The addition of NART to NACT could result in a higher rate of pCR, although our study was too small to determine this difference. A recent propensity score matched case-control analysis of 32 patients, receiving concomitant NART and docetaxel after neo-adjuvant FEC, found a significant increase in pCR from 14% to 22% by adding NART [35]. These pCR rates are a lot lower than in our study, most likely since they included mostly Luminal A and B patients. Further studies are required to investigate if NART results in a higher pCR, which could result in better survival outcomes [42].

Other potential advantages of NART are better targeting of the dose, higher biological effectiveness of RT and the induction of an anti-tumor immune response [43]. Firstly, delineation of the tumor in situ (GTV), instead of the postoperative tumor bed, should reduce the high dose volume to healthy tissue, improving cosmesis and reducing radiotherapy toxicity. The use of NART has been found to reduce the PTV volume in partial breast irradiation [44]. This difference was not reflected in the CTV or PTV boost volumes between both treatments in our study. However, in the NART arm on average 21% of the PTV boost volume compromised of the GTV, i.e. malignant tissue that will be surgically removed. Moreover, the chance of accurate boost delineation is higher when the tumor is

Table 1
Baseline characteristics.

	Intervention group	Control group	p-value
	N = 10	N = 9	
Age - mean (range) – yr	55 (31–67)	54 (41–64)	0.89
BMI - mean (range)	26,1 (19,3–37,0)	25,6 (22,8–33,9)	0.82
Laterality			
Left	3 (30%)	3 (33%)	0.88
Right	7 (70%)	6 (67%)	
cTNM classification			
T1cN0	2 (20%)	0 (0%)	0.41
T1cN1	1 (10%)	1 (11%)	
T2N0	5 (50%)	5 (56%)	
T2N1	1 (10%)	3 (33%)	
T3N1	1 (10%)	0 (0%)	
Tumor diameter on pre-treatment MRI – mean (range) - mm	3,4 (1,9–5,7)	3,4 (1,4–6,5)	0.97
Lymph node irradiation			
Yes	4 (40%)	5 (56%)	0.82
No	6 (60%)	4 (44%)	
Clinicopathological subtype			
Luminal A	1 (10%)	0 (0%)	0.82
Luminal B	2 (20%)	2 (22%)	
Her2+	3 (30%)	3 (33%)	
Basal like	5 (50%)	4 (44%)	

Table 2
Treatment durations according to the number of days from diagnostic biopsy for each individual patient.

Patient number	First treatment	Start NACT	Surgery	Last treatment
Intervention group (n=10)				
2[a]	22[a]	22[a]	175[a]	220[a]
4	34	49	222	222
6	27	43	223	223
8	27	48	204	204
10	33	50	208	208
12	45	62	214	228[b]
15	24	56	200	200
17	32	50	229	229
19	29	49	198	253[b]
20	31	48	196	196
Mean (sd)	**31 (6)**	**48 (10)**	**207 (16)**	**218 (12)**
Control group (N=9)				
1	37	37	197	239
5	29	29	189	234
7	25	25	200	252
9	27	27	188	233
11	41	41	218	268
13	21	21	166	211
14	22	22	177	241
16	18	18	172	217
18	21	21	174	241
Mean (sd)	**27 (8)**	**27 (8)**	**187 (16)**	**237 (17)**

NACT: neo-adjuvant chemotherapy; NART: neo-adjuvant radiotherapy.
[a] Patient did not receive NART but adjuvant radiotherapy.
[b] Patient received additional surgery.

still visible on the imaging.

Secondly, NART has shown signs of higher effectiveness through better local control, and possibly even survival, in other tumor types [45–48]. Retrospective studies in breast NART support this hypothesis of better outcomes after NART, although recent prospective data are lacking [6,38]. From a radiobiology perspective, the intact vasculature, lower hypoxia and reduction in radioresistant tumor clones would be expected to result in better radiosensitivity. Thirdly, NART can induce antigen release, increasing the presence of antigen-presenting cells and stimulating T-cell response [49].

The main disadvantage of NART, in combination with NACT, is the uncertainty of the influence of NART on treatment escalation after NACT. Recent trials have shown advantages when escalating treatment after incomplete response, in TNBC and Her2+ tumors [2,3]. Further research is required to better select patients requiring adjuvant systemic treatment using biomarkers or liquid biopsies, evolving from the approach of using the patients as their own tumor model. Nevertheless, these techniques are not yet ready for prime time [50]. Liquid biopsies, to detect extracellular vesicles, have been collected for future research. A major challenge of NART is predicting which patients require axillary RT. A negative axilla on imaging does not preclude the finding of a positive sentinel node at the time of surgery. A pre-SLNB is one solution, but it is difficult to schedule and requires 2 surgical procedures. Another potential disadvantage of sequential NART is the NACT delay. In our trial the average duration between the first fraction of NART and the first cycle of NACT was only 19 days, although NACT after diagnosis was delayed, on average, by 21 days. To our knowledge no studies are published investigating the impact of NACT delay on survival. In the adjuvant setting, CT delays above 30 days have been associated with worse overall and disease free survival, especially in TNBC [25,27]. In an umbrella trial, Khorana et al. found a significant impact of time to treatment initiation with any treatment modality [19]. As mentioned previously, treatment initiation was not significantly different between both arms (31 vs 27 days).

This pilot trial is the first study to use a 5-fraction RT schedule in the neo-adjuvant setting, showing that the combination is feasible and leads to no excess acute toxicity, although it has a limited sample size of 20 patients. Furthermore, the combination of NART in 5 fractions and modern NACT consisting of anthracyclines and taxanes is achievable. However, many questions regarding NART in 5 fractions in combination with NACT remain unanswered. Radiotherapy in 5 fractions has not been investigated in a population of patients with breast cancer who received NACT. Therefore, more evidence is required to confirm this protocol is safe in terms of survival in this population. The optimal sequence of current (neo-) adjuvant treatments remains uncertain [51]. NART results in a shorter OTT since the waiting time after surgery can be reduced and post-operative complications do not result in delays of treatment. Often RT cannot be delivered within 8 weeks from the first surgery, as was the case in the control arm for 2 patients requiring a mastectomy and additional surgery, which has been correlated with worse disease free and overall survival [23]. In the NACT setting,

Table 3
Neo-adjuvant treatment response rate, surgery and radiotherapy details.

	Intervention group	Control group	P-value
Pathological complete response	N = 10	N = 9	
Yes	6 (60%)	6 (67%)	1.0
No	4 (40%)	3 (33%)	
Chemotherapy			
Finished all EC and Taxol treatments			
Yes	7 (70%)	4 (44%)	0.37
No	3 (30%)	5 (56%)	
Surgery			
Mastectomy rate			
Yes	1 (10%)	2 (22%)	0.58
No	9 (90%)	7 (78%)	
Second surgery			
Yes	2 (20%)	2 (22%)	1.0
No	8 (80%)	7 (78%)	
Use of antibiotics 3 weeks after surgery			
Yes	3 (30%)	0 (0%)	0.21
No	7 (70%)	9 (100%)	
Radiotherapy			
CTV boost volume in CC (mean (sd))	38 (25)	33 (11)	0.59
PTV WBI-volume in CC (mean (sd))	713 (333)	793 (304)[a]	0.62

NACT: neo-adjuvant chemotherapy treatment; PTV planning target volume.
[a] The data of only 7 patients is available, since 2 patients received a mastectomy after NACT.

further investigation is required to determine the impact of NART, with or without immunotherapy, on pCR and survival. Hence, our pilot trial was underpowered for these outcomes. Increasing pCR can potentially result in a de-escalation of adjuvant treatment, especially in the setting of Her2+ and TNBC [2,3]. Several trials are investigating this scenario, notably the NeoChack-Ray trial (NCT03875573) investigates the impact on pCR from adding RT and immunotherapy to NACT in luminal B patients. Also, the PANDoRA trial (NTC03872505) compares non-anthracycline-based NACT and immunotherapy with our without NART for pCR [52]. Furthermore, concomitant delivery of NACT and NART, in an accelerated 5-fraction schedule with SIB, could be investigated to further reduce OTT, but increased acute and long-term toxicity are to be expected.

This pilot trial confirms that accelerated NART in 5 fractions with simultaneously integrated boost (SIB) is feasible and results in a shorter OTT without excess acute toxicity.

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Declaration of competing interest

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