10-Year oncological outcome report after second conservative treatment for ipsilateral breast tumor event

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A R T I C L E   I N F O

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A B S T R A C T

Purpose: To analyze long-term oncological outcome after 2nd conservative treatment (2ndCT) for patients with ipsilateral 2nd ipsilateral breast tumor event (2ndIBTE).

Materials/methods: In this retrospective observational study (N=244), patients with 2ndIBTE underwent 2ndCT (lumpectomy + tumor bed re-irradiation). 3rdIBTE (3rdIBTE-FS), regional relapse- (RRFS) and metastatic disease- (MD-FS) free survivals as well as disease-free (DFS), specific (SS) and overall (OS) survival were analyzed. Late toxicity was reported.

Results: Between 09/2000 and 04/2022, 244 patients presented a 2ndIBTE and underwent a 2ndCT. Among them, 113 pts with a minimum follow-up of 60 months were analyzed. Median time interval between 1st and 2ndIBTE was 13.5 years [2–35]. Median 2ndIBTE age was 66.2 years [31–85]. 2ndIBTE were adenocarcinomas (77 %). Tumor size was <20 mm (86.7 %). 2ndIBTE were grade 1/2 (75 %), with positive hormonal receptor (85 %) and clear surgical margins (no ink on tumor, 90.3 %). In the APBI classification, 21 pts were high-risk (18.6 %), while 100 pts were low-risk (71.4 %), 22 pts intermediate-risk (18.6 %). Median 2ndCT was 121.5 months [95%CI 111.7–129.6]. In multivariate analysis, APBI classification (high-risk; HR2.66 [1.01–6.8], p = 0.049) and tumor size (≥20 mm; HR2.64 [1.02–6.8], p = 0.045) were considered independent prognostic factors for DFS. Ninety-seven late complications were observed (fibrosis 64 %) with 6.2 % G ≥3 late toxicity. Cosmetic outcome was excellent/good in 91.2 %.

Conclusions: With long follow-up, 2ndIBTE managed with 2ndCT allows second breast preservation without oncological outcome compromise and acceptable G ≥3 toxicity.

Abbreviations: 1stCT, first conservative treatment; 1stIBTE, first ipsilateral breast tumor event; 2ndCT, second conservative treatment; 2ndIBTE, second ipsilateral breast tumor event; 3rdIBTE-FS, third ipsilateral breast tumor event; 3rdIBTE-FS, third ipsilateral breast tumor event free survival; 95%CI, 95% confidence interval; APBI, accelerated and partial breast irradiation; APBI, accelerated and partial breast re-irradiation; CTCAE, Common Toxicity Criteria for Adverse Events; CTV, clinical target volume; DFS, disease-free survival; ESMO, European Society for Medical Oncology; GEC-ESTRO, Groupe Européen de Curiethérapie European Society for Radiotherapy and Oncology; HDR, high-dose rate; LDR, low-dose rate; MDFS, metastatic disease-free survival; MFU, median follow-up; MIB, multi-cather interstitial brachytherapy; OS, overall survival; RRFS, regional recurrence free survival; SM, salvage mastectomy; SS, specific survival.

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(280,000 and 700,000 in 2040) [7]. These data suggest that the number of patients experiencing a second ipsilateral breast tumor event (2ndIBTE) will increase dramatically during the next decades. This represents a major public health issue as well as a crucial concern for patients, health care providers and insurances.

Currently, for a patient experiencing a 2ndIBTE, mastectomy appears generally to be the first proposed salvage treatment option although encouraging results after second conservative treatment (2ndCT) combining lumpectomy plus tumor bed reirradiation have been reported based on large retrospective or prospective studies [8–10]. Recently, the Breast Cancer Working Group of the GEC-ESTRO reported the results of a propensity score-matched cohort analysis comparing salvage mastectomy (SM) or 2ndCT and confirmed the absence of significant difference in terms of oncologic outcome between the two salvage treatment options [11].

Although more and more consistent data bearing out 2ndCT as a valuable alternative to SM are now available, in the case of 2ndIBTE, the lack of long-term data after salvage conservative procedure represents a potential issue. The aim of this study was to report long-term results after 2ndCT for patients with 2ndIBTE.

Materials and methods

This observational, single-institution, retrospective study was performed in the Antoine Lacassagne Center (Nice, France). Data were collected from patients’ files. Consent of each patient was obtained prior to data collection and analysis, after having received clear and fair information on the use of the data. This study was approved by the local ethics committee. In accordance with current legislation, data collection was registered at the National Health Data Hub under the number N° F20210402152843.

Patient features

The target population was women presenting a 2ndIBTE occurring after a radio-surgical conservative treatment performed for the primary tumor (1stIBTE). Second IBTE was defined as a new oncological event occurring within the pre-treated breast, at least 1 year after the 1stIBTE, excluding in-breast skin and sub-cutaneous metastatic diseases. Second CT combining salvage lumpectomy plus accelerated partial breast re-irradiation (APBrI) was proposed. APBrI consisted in multi-catheter interstitial brachytherapy (MIB) using either low- (LDR) or high-dose rate (HDR).

Patients with SM indication (multicentric tumor, major late toxicity after 1stCT, cup A breast size, or patient’s wish) were not considered for this study. Second CT was proposed as an alternative for patients reluctant to undergo SM, irrespective of GEC-ESTRO APBI risk-group classification status [12]. Consequently, patients with some poor prognostic factors (lympho-vascular invasion, extensive intra-ductal component, high Ki67, poor differentiation, Her2 over-expression or triple negative molecular status ...) were also considered eligible for 2ndCT. All patients received detailed information concerning risks and benefits of the salvage treatment procedures.

Treatment features

The 2ndCT process has already been described [12]. Briefly, it consisted in a lumpectomy with clips clamped into the lumpectomy cavity. Axillary lymph node assessment (dissection or sentinel lymph node) was not systematically performed for patients who already underwent axillary dissection at the time of primary treatment.

Regarding APBrI procedure, vector implantation was performed intra- or postoperatively following the Paris System geometric recommendations [13]. From 2000 until 2004, patients underwent LDR brachytherapy (intra-operative procedure). After 2004, all the APBrI were performed by using HDR brachytherapy (local anesthesia for post-operative implant). The prescribed dose was 46 Gy and 32 to 34 Gy (in 8 to 10 fractions delivered twice daily over 5 consecutive days, during an ambulatory procedure) for LDR and HDR brachytherapy respectively.

Adjuvant treatments (hormonal therapy, chemotherapy, or anti-Her2-targeted therapy) were used according to our center guidelines.

Follow-up

One month after brachytherapy, patients were systematically examined by the radiation oncologist for early toxicity evaluation. Then, patients were seen every 6 months alternatively by the surgeon, the medical and radiation oncologist with clinical examination and yearly mammogram. Third IBTE- (3rdIBTE-FS), regional relapse- (RRFS) and metastatic disease- (MDFS) free survival as well as disease-free (DFS), specific (SS) and overall survival (OS) were analyzed. Late toxicity was investigated using the Common Classification for Adverse Events 4.0. Cosmetic results were reported by the radiation oncologist based on the Harvard criteria [14].

Statistical analysis

Description of the study population and the different parameters investigated was made using absolute and relative frequencies for the qualitative data and summarized using descriptive statistics such as median, extreme for quantitative data. Statistical comparisons were performed using the y2 test for qualitative data and non-parametric matched pairs Wilcoxon test for quantitative data. Third IBTE-FS, RRFS and MDFS were calculated between the date of 2nd surgery and these respective events and were estimated using the Kaplan–Meier method. DFS, SS and OS were defined as the time between the date of 2nd surgery and any oncological outcome and death due to all causes, death due to breast cancer and death due to any cause respectively. Patients still alive at the last visit were censored at the date of last follow-up. Median follow-up with 95 % confidence intervals was calculated by reverse Kaplan–Meier method. In univariate analysis, the survival curves were compared using the log-rank test. In multivariable analysis, association between several parameters and oncological outcome was expressed as a hazard ratio with a 95 % confidence interval, which was estimated with the use of a Cox proportional hazards model. Because APBI and Molecular classifications are based on different but complementary items, a new variable was generated named [APBI/Molecular] classification. The latter is the combination of the 3 risk-groups of ABPI classification [15] and the 3 categories of the molecular classification [16] (e-Table 1, supplementary data). Collinearity between variables entered in the model was evaluated using the ‘r’ Pearson correlation coefficient. If r > 0.40, one of the two variables was considered as redundant and had to be removed from the model. Proportional hazards were verified for all entered variables. All p values inferior to 0.05 (two-sided) were considered statistically significant. All statistical analyses were performed in 5 % alpha risk using R 3.2.2 software on Windows®.

Results

Patient, tumor and treatment features

Between 09/2000 and 04/2022, 244 patients (pts) with 2ndIBTE underwent a 2ndCT combining lumpectomy plus APBrI. Among them, 113 pts were analyzed in order to evaluate long-term oncological outcome with a minimum follow-up of 60 months for the last included patient. Median time interval between 1st and 2nd surgery was 13.5 years [2–35]. Patient features for 2ndIBTE are summarized in Table 1. Median age was 49.1 years [24–83] and 66.2 years [31–85] for 1st and 2ndIBTE, respectively. Second IBTE were mostly adenocarcinomas (77%), occurring mainly in or in the vicinity of the primary tumor bed (79%). Median tumor size was 10 mm [7–15] and < 20 mm in 86.7 %. <5 %
Table 1
Patient and treatment features at the time of 2\textsuperscript{nd} IBTE (113 pts).

| Items | # | % / [min – max] 95CI |
|-------|---|---------------------|
| Median age @ primary (years) | 49.1 | [44-59] |
| Median age @ 2\textsuperscript{nd}IBTE (years) | 66.2 | [59.7 – 71.2] |
| Time interval between 1st/2nd surgery (years) | 13.5 | [2–35] |
| MFU (months) | 121.5 | [111.7 – 129.6] |
| Salvage surgery period | | |
| ≤ 2001 | 10 | 8.8 |
| ≥ 2002 / ≤ 2009 | 54 | 47.8 |
| > 2010 | 49 | 43.4 |
| 2\textsuperscript{nd} IBTE site | | |
| In the PTB | 54 | 47.8 |
| Vicinity of the PTB | 35 | 31.0 |
| At distance from the PTB | 18 | 15.9 |
| Unknown | 6 | 5.3 |
| Histological type | | |
| Invasive ductal carcinoma | 87 | 77.0 |
| Invasive lobular carcinoma | 15 | 13.3 |
| Ductal carcinoma in situ | 10 | 8.8 |
| Another invasive carcinoma | 1 | 0.9 |
| Median tumor size (mm) | 10.0 | [7–15] |
| < 20 mm | 98 | 86.7 |
| ≥ 20 mm | 15 | 13.3 |
| Axillary status | | |
| pN0 | 5 | 4.4 |
| pN1 | 0 | 0 |
| pNx | 108 | 95.6 |
| Histological grade | | |
| 1 | 33 | 29.2 |
| 2 | 52 | 46.0 |
| 3 | 21 | 18.6 |
| Unknown | 7 | 6.2 |
| Hormonal receptor status | | |
| Positive | 96 | 85.0 |
| Negative | 8 | 7.0 |
| Unknown | 9 | 8.0 |
| Her2 status | | |
| Non-over-expressed | 94 | 83.2 |
| Over-expressed | 5 | 4.4 |
| Unknown | 14 | 12.4 |
| Clear surgical margins | | |
| Yes | 102 | 90.3 |
| No | 11 | 9.7 |
| Lympho-vascular involvement | | |
| No | 82 | 72.6 |
| Yes | 5 | 4.4 |
| Unknown | 26 | 23.0 |
| Extensive intra-ductal component | | |
| No | 89 | 78.8 |
| Yes | 10 | 8.8 |
| Unknown | 14 | 12.4 |
| GEC-ESTRO APBI classification | | |
| Low | 42 | 37.2 |
| Intermediate | 50 | 44.2 |
| High | 21 | 18.6 |
| Molecular classification | | |
| HR+/Her2- | 87 | 77.0 |
| HR+/Her2+ | 5 | 4.4 |
| Triple negative | 6 | 5.3 |
| Unknown | 15 | 13.3 |
| APBI/Molecular classification | | |
| 2 [1 + 1] | 34 | 30.1 |
| 3 [2 + 1 / 1 + 2] | 38 | 33.6 |
| 4 [1 + 3 / 3 + 1 / 2 + 2] | 24 | 21.2 |
| 5 [2 + 3 / 3 + 2] | 2 | 1.8 |
| 6 [3 + 3] | 0 | 0 |
| Unknown | 15 | 13.3 |

Table 1 (continued)

| Items | # | % / [min – max] 95CI |
|-------|---|---------------------|
| No 19 | 16.8 |
| Trastuzumab | 98 | 86.7 |
| Yes | 15 | 13.3 |
| 9 pts (8 %) and 1pt (0.8 %) respectively. Dosimetric data are reported in e-Table 2 supplementary data.

Oncological outcome

With a median follow-up (MFU) of 121.5 months [95 %CI 117.7 – 129.6], 10 pts (8.8 %) developed a 3\textsuperscript{rd} IBTE after 2\textsuperscript{nd}CT leading to a 10-year 3\textsuperscript{rd} IBTE-free survival rate of 89 % [95 % CI 83 – 96] (Fig. 1A). Four patients (3.5 %) presented a regional relapse, and metastatic disease progression was observed for 10 pts (8.8 %). A total of 5 pts (4.4 %) died, while cause of death was breast cancer for 4 pts. Then-year RRFS, MDFS, DFS, SS and OS rates were 94 % [95 % CI 89 – 100], 89 % [95 % CI 83 – 96], 78 % [95 % CI 70 – 87], 95 % [95 % CI 91 – 100] and 94 % [95 % CI 90 – 99] respectively (Table 2; Fig. 1B-1F).

According to the GEC-ESTRO APBI classification, 42 pts (37.2 %), 50 pts (44.2 %) and 21 pts (18.6 %) were low-, intermediate- and high-risk respectively (Table 1). Third IBTE rates were 4.8 %, 12 % and 23.8 % for low-, intermediate- and high-risk pts respectively (p = 0.021) (Fig. 2A). For molecular classification, 87 pts (77 %), 5 pts (4.4 %) and 6 pts (5.3 %) were HR+/Her2-; HR+/Her2+ and Triple negative respectively (15 pts [13.3 %] unknown), while all the 3\textsuperscript{rd} IBTEs were observed in the HR+/Her2- group. Regarding [APBI/Molecular] classification (e-Table 1, supplementary data), 34 pts (30.1 %), 38 pts (33.6 %), 24 pts (21.2 %) and 2 pts (1.8 %) were scored 2, 3, 4 and 5 respectively (np with st score 6). Third IBTE rates were 8.3 % and 15.4 % for score ≤ 3 and score ≥ 4 respectively (p = 0.152) (Fig. 2B).

In univariate analysis, APBI classification and tumor size were prognostic factors for 3\textsuperscript{rd} IBTE-FS (p = 0.021; p = 0.048 respectively) and for DFS (p = 0.05; p = 0.012 respectively). In multivariate analysis, APBI classification (low vs high-risk; HR 2.64 [95 %CI 1.02 – 6.8], p = 0.049) and tumor size (<20 mm vs ≥ 20 mm; HR 2.64 [95 % CI 1.02 – 6.8], p = 0.045) were considered independent prognostic factors for DFS (e-Table 2, Supplementary data).

Toxicity profile and cosmetic outcome

Among the 113 pts, at the last follow-up, 97 late complications were observed after 2\textsuperscript{nd}CT. Cutaneous (36.1 %) and subcutaneous (27.8 %) fibrosis were the most frequent late side effects (Table 3). The rates of late grade 3 and 4 toxicities were 5.2 % and 1 % respectively.

Regarding cosmetic outcome analyzed in the 113 pts, excellent, good, fair and poor results were observed in 70 pts (62 %), 33 pts (29.2 %), 9 pts (8 %) and 1pt (0.8 %) respectively. Dosimetric data are reported in e-Table 2 supplementary data.
Discussion

The analysis of our real-world cohort of patients with a non-metastatic 2nd IBTE, 2nd CT based on breast-conserving surgery plus APBr1 (MIB) provide consistent data regarding long-term oncological outcome. To our knowledge, the present study is the first population-based analysis reporting oncologic results of 2nd CT with a MFU of 10 years.

For patients experiencing a 2nd IBTE, 2nd CT represents a de-intensification of breast cancer treatment. In this context, the European Society for Medical Oncology (ESMO) recently considered that a non-inferiority randomized phase 3 trial represents the best methodological approach for achieving the highest proof level [17]. However, such a trial comparing SM versus 2nd CT requires enrolment of about 3600 pts in all and would be difficult to perform [11]; the best way to compare these two salvage therapeutic options is thus to use a propensity score-matching method [18]. The results of the latter were recently published by GEC-ESTRO confirming that oncological outcomes between SM and 2nd CT were not significantly different and consequently, both salvage options could be discussed [11]. These findings are all the more important given that mastectomy (even with a surgical reconstruction) has a negative impact on body image, self-confidence and quality of life [19]. Mastectomy is even associated with a higher rate of unemployment [20]. Furthermore, de Boniface J et al, shown that for T1-2 N0-2 primary breast cancers, breast-conserving surgery plus whole breast irradiation showed improved 6-year specific and overall survival [21]. These results were confirmed by van Maaren MC et al, at 10 years for early breast cancer [22].

Long term FU is warranted due to the continuous occurrence of oncological events. Indeed, while the 5-y 3rd IBTE cumulative event rate was 0.9 %, comparable to the results of APBI GEC-ESTRO and IMPORT-Low phase 3 trials [23,24], it rose to 8.8 % at 10 years, close to the results provided by START and Ontario hypofractionated phase 3 trials [4,25]. These data show that, in our cohort, with a median time interval between 1st and 2nd IBTE of 13.5 years, long-term local control after 2nd CT appears comparable to the 10-y results obtained after radiosurgical treatment for primary T1-2 breast cancers.

Regarding OS, the results presented at 5 (100 %) and 10 (94 %) years appear slightly better compared to those published after conservative treatment.

Table 2
5- and 10-year oncological outcomes after second conservative treatment.

| Oncological outcomes | # Cumulative events | @5 years (%)/[min – max] 95 %CI | # Cumulative events | @10 years (%)/[min – max] 95 %CI |
|----------------------|---------------------|--------------------------------|---------------------|--------------------------------|
| 3rd IBTE-FS          | 1/113 (0.9 %)       | 98 [96 – 100] %                  | 10/113 (8.8 %)      | 93 [90 – 99] %                  |
| RR-FS                | 0/113 (0 %)         | 100 [100 – 100] %                | 4/113 (3.5 %)       | 94 [89 – 100] %                 |
| MD-FS                | 4/113 (3.5 %)       | 10/113 (8.8 %)                  | 96 [93 – 100] %     | 93 [90 – 99] %                  |
| DFS                  | 4/113 (3.5 %)       | 20/113 (17.7 %)                 | 96 [93 – 100] %     | 93 [90 – 99] %                  |
| SS                   | 0/113 (0 %)         | 100 [100 – 100] %                | 4/113 (3.5 %)       | 95 [91 – 100] %                 |
| OS                   | 0/113 (0 %)         | 100 [100 – 100] %                | 5/113 (4.4 %)       | 94 [90 – 99] %                  |

3rd IBTE-FS: Third ipsilateral breast tumor event free survival; RR-FS: Regional relapse free survival (axilla and internal mammary chain area); MD-FS: Metastatic disease-free survival; DFS: Disease free survival; SS: Specific survival (Any breast cancer-related event includes local, regional, or distant relapse, or breast cancer death, or death from any cause); OS: overall survival.
treatment for primary breast cancers [4,23–25]. However, assuming the fact that our cohort remains smaller compared to the others, the minimum follow-up of the patients was 60 months excluding de facto all the "early" deaths occurring within the first 5 years after 2ndCT. But this apparent patient selection highlights the selection criteria for achieving optimal oncological outcome after 2ndCT for 2ndIBTE. Indeed, in our cohort, patients were mainly at low or intermediate risk in the APBI classification (81.4 %) with a HR+/Her2-molecular status in 77 %. (e-Table 3, Supplementary data). In multivariate analysis, the GEC-ESTRO study showed that tumour size (≥ 30 mm) and time between 1st and 2ndIBTE (< 36 months) were independent prognostic factors for MDFS, DFS, SS and OS [11]. Time between 1st and 2ndIBTE is a critical point strongly correlated to the characterization of 2ndIBTE as "true recurrence" (early breast event) or "new primary" (late breast event) and, as a consequence, to MDFS [26]. In this cohort, due to a 5-y minimum FU, "true recurrences" were rare leading to a better final oncological outcome (MDFS, OS). We also reported a rate of adjuvant chemotherapy of 13.3 %, while the indication was mainly based on histo-prognostic factors without taking into account the local recurrence context. Currently, little data are available regarding the use of chemotherapy for "true recurrences". CALOR phase 3 trial analyzed the efficacy of chemotherapy according to hormonal receptor status for isolated 2ndIBTE and noticed a significant increase of DFS and OS for hormonal negative patients with a median time between 1st and 2ndIBTE of 3 years [27].

This analysis contains some limitations. As in all retrospective observational studies, our results could have been influenced by unknown residual confounding. During the long study period, diagnostic methods and therapeutic strategies for 2ndIBTE evolved, leading us to assume that some patients did not benefit from current treatment options (repeat sentinel lymph node biopsy or systemic therapies). The absence of some data could be considered a limitation. For example, data from primary tumours were not systematically and exhaustively recorded, mainly for 2ndIBTE occurring before 2005. Also, comorbidities which could have had a competitive impact on clinical outcome were not taken into account. Nevertheless, we believe that our key message remains unaffected.

Conclusion

This first report of long-term clinical outcome after 2ndCT for 2ndIBTE provides new consistent clinical data for the implementation of conservative treatment as a validated salvage therapy. These findings can inform the decision-making process for patients, health care providers and possibly health insurances. Currently, MIB based APBrI provides the most consistent data with the longest follow-up. However, investigations are currently ongoing into different re-irradiation techniques which could encourage the spread of 2ndCT for patients who refuse mutilating salvage therapy.

Patient informed consent statement

Before data collection, the consent of all patients was obtained National Health Data Hub data collection number: F20210402152843.

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Table 3
Late complications (type and grade) for the 113 evaluable patients.

| Complications          | # Events | %  |
|------------------------|----------|----|
| **Type**               |          |    |
| Cutaneous fibrosis     | 35       | 36.1 |
| Sub-cutaneous fibrosis | 27       | 27.8 |
| Telangiectasia         | 13       | 13.4 |
| Hyper-pigmentation     | 4        | 4.1  |
| Ulceration             | 2        | 2.1  |
| Deformation            | 16       | 16.5 |
| Total                  | 97       | 100  |
| **Grade**              |          |    |
| 1                      | 54       | 55.7 |
| 2                      | 37       | 38.1 |
| 3                      | 5        | 5.2  |
| 4                      | 1        | 1.0  |
| Total                  | 97       | 100  |
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.10.008.

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