

# Accelerated Partial Breast Irradiation in the Elderly: 8-year Oncological Outcome and Prognostic Factors

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## Research

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# Abstract

**Introduction:** To evaluate long term clinical outcome and prognostic factors after accelerated partial breast irradiation (APBI) in the elderly using high-dose-rate interstitial multi-catheter brachytherapy (HIBT).

**Material and methods:** Between 2005 and 2018, 109 patients underwent APBI using HIBT (34 Gy/10f/5d or 32 Gy/8f/4d). Based on a prospective database, outcomes were retrospectively analyzed (local relapse-free survival (LRFS), metastatic-free survival (MFS), specific survival (SS) and overall survival (OS). Prognostic factors were investigated. Late toxicity and cosmetic evaluation were reported.

**Results:** With a median follow-up of 97 months [7–159], median age was 81.7 years [58-89]. According to the GEC-ESTRO APBI classification, 72.5%, 11.9% and 15.6% were classified as low, intermediate and high-risk respectively. The histological type was mainly invasive ductal carcinoma (87.1%). The median tumor size was 10 mm [range 1-35]. Eight-year LRFS, SS and OS were 96.7% [95% CI [0.923; 1]], 96.7% [95% CI [0.924; 1] and 72%[95% CI [0.616; 0.837] respectively. In univariate analysis, APBI classification was not considered as prognostic factor, while molecular classification was prognostic factor for OS ( $p < 0.0001$ ), SS ( $p = 0.007$ ) and MFS ( $p = 0.009$ ) but not for LR ( $p = 0.586$ ). No Grade  $\geq 3$  late toxicity was observed while 61 patients (88.4%) and 8 patients (11.6%) presented grade 1 and 2 toxicities respectively. Cosmetic outcome was excellent/good for 96.4%.

**Conclusion:** Long-term follow-up confirms that HIBT is safe and effective for elderly early breast cancer. Our results suggest that selected elderly women presenting with high-risk breast cancer could be also considered for APBI.

## Introduction

Breast cancer has been recognized as a major public health problem for many years. The global incidence of breast cancer has been rising with an average annual increases of 3.1%, beginning with 641,000 cases in 1980 and increasing to about 2.1 million in 2018 (1). Currently, life expectancy is growing and the incidence of breast cancer in women increases with age. An aging population could explain in part why more than 40% of breast cancers occur in women over 65 years (2).

A meta-analysis of randomized studies with 10,801 patients showed that radiation therapy (RT) after breast-conserving surgery reduces the risk of all recurrences including ipsilateral breast tumor recurrence and improves overall survival (OS) by increasing breast cancer-specific survival (3). However, for elderly women specifically, whole breast irradiation (WBI), which can last 6–7 weeks or 4–5 weeks in case of a hypofractionated regimen, may be challenging to perform due to their potential comorbidities and the treatment inconveniences (4–6). In order to reduce discomfort and expenses induced by adjuvant RT in low-risk breast cancer (elderly/postmenopausal women), 5 randomized trials comparing adjuvant endocrine therapy alone with or without post-operative external WBI were conducted. They confirmed that a combined treatment does not significantly impact on OS rate, while it significantly reduces the rate of

local recurrence (LR) (7–12). Based on these results, the National Comprehensive Cancer Network concluded that RT could be omitted in women aged 70 and older with hormonal receptor (HR) positive stage I breast cancer, receiving endocrine therapy, while, in some cases, a non-compliance with endocrine therapy is observed due to its side effects (13).

For the elderly, is it possible to propose a compromise between WBI, which is a long but efficient treatment in terms of local control, and endocrine therapy as a sole adjuvant treatment, but with significant associated risks in terms of LR? During the last decade, accelerated and partial breast irradiation (APBI) techniques have emerged, as an attractive alternative to WBI for patients with early breast cancer and low-risk of LR (14–16). The volume of breast tissue irradiated is smaller, the course of treatment is shortened and therefore is generally a more suitable treatment for elderly patients (17,18). APBI appears to be an appropriate solution, decreasing the risk of LR rate whilst, at the same time, preserving oncological outcome and quality of life as well as reducing expenses for the healthcare reimbursement system.

We have previously reported the 5-year clinical outcome of a cohort of elderly women treated with APBI based on a high-dose rate interstitial multicatheter brachytherapy (HIBT), but a longer follow-up was needed to assess the consistency of our results. The aim of this report was to update the clinical outcome after APBI in our previously published cohort and discuss prognostic factors (19).

## **Material And Method**

All materials and methods sections were previously described in details (19).

This observational, single-center, retrospective study was performed in the Antoine Lacassagne Center in Nice, France, from 2005 to 2018. Data were collected from patients' files.

## **Patient features**

Target population were women who underwent breast conservative surgery. All along the study period, the Bethesda workshop (20) and then the GEC-ESTRO recommendations (21) were used for the selection of elderly women who could be good candidates for adjuvant APBI using HIBT. However, for some frail patients presenting comorbidity factors, APBI was proposed without strong adherence to the APBI recommended criteria. This study was approved by the Institutional Review Board of Antoine Lacassagne Cancer Centre (n°17013) which approved the ethical aspect of the protocol. The board waived the requirement for informed consents because of the retrospective design of this study.

## **Treatment features**

### **Breast surgery**

Patients underwent lumpectomy with axillary management through sentinel lymph node or axillary dissection. Four to five clips were clamped by the surgeon to mark the tumor bed before closing the

lumpectomy cavity.

## Brachytherapy

Vector implantation for HIBT was performed pre- or postoperatively following the Paris System geometric recommendations (22). The implant was performed under local anesthesia in case of post-operative procedure. A post-implant CT-scan was performed in order to delineate the clinical target volume (CTV). The CTV delineation consisted in an expansion of 1 cm around the clips. The CTV was redefined as 5 mm below the skin-surface and 5 mm above the underlying ribs for superficial and deep tumors, respectively (23,24).

The dose distribution was optimized manually by varying time and stop position of the radio-active source. Dose constraints were: dose delivered to 90% of the CTV more than 105% ( $D_{90} > 105\%$ ), part of the CTV receiving 100% of the prescribed dose more than 95% ( $V_{100} > 95\%$ ),  $V_{150} < 35\%$ ,  $V_{200} < 15\%$  (with no confluence of two consecutive  $V_{200}$  isodoses and  $V_{200}$  isodose diameter  $< 10$  mm) and  $DM_{skin}$  (maximal dose delivered to the skin)  $< 75\%$ . Two protocols were applied delivering 2 fractions per day, 6 hours apart, up to a total dose of 34 Gy (3.4 Gy/fraction over 5 consecutive days) or 32 Gy (4 Gy/fraction over 4 consecutive days). Irradiation was performed with an after-loading device using a 10 Ci  $^{192}\text{Ir}$  source (Microselectron™; Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden and Saginova™, Eckert and Ziegler BEBIG company, Berlin, Germany). The irradiation was performed in an out-patient hospitalization way.

## Adjuvant treatments

Endocrine therapy, chemotherapy, or anti-HER2-targeted therapy were used according to our center guidelines.

## Follow-up

All patients were followed up closely. Patients were systematically examined by the radiation oncologist one month after brachytherapy to evaluate early toxicity. Afterwards, patients were seen every 6 months by the surgeon, the medical or radiation oncologist, during a clinical examination. Mammograms were obtained yearly. Late toxicities evaluation used the Common Classification for Adverse Events 4.0. Cosmetic results were assessed at every follow-up visit by the physician according to the Harvard criteria (25): excellent (treated breast nearly identical to untreated breast), good (treated breast slightly different from untreated), fair (treated breast clearly different from untreated but not seriously distorted), and poor (treated breast seriously distorted). All patients were included in the follow-up. The median follow-up was calculated from the day of last brachytherapy fraction to the date of the last follow-up.

## Statistical analysis

Data were analyzed using the R 3.5.1 Windows software. The description of the study population and the different parameters consisted of absolute and relative frequencies for qualitative data, and descriptive statistics such as median and range for quantitative data. Local recurrence-free survival (LRFS) was

defined as the time between the date of surgery and the date of ipsilateral LR. Metastatic disease-free survival (MFS) rate was defined as the time between the date of surgery and the date of metastatic disease occurrence. Specific survival (SS) and OS were defined as the time between the date of surgery and death from cancer or any cause respectively. These data were estimated and plotted at different time intervals with their 95% confidence using the Kaplan-Meier method. Patients were censored at the time of death or at last follow-up. In univariate analysis, the survival curves were compared using the log-rank test. The level of significance was set at a p-value of less than 0.05. Univariate and multivariate analysis were performed in order to find some independent prognostic factors for oncological outcomes (LRFS, MFS, SS, OS).

## Results

### Patient and tumor characteristics

Between January 2005 and December 2018, 109 patients were treated with APBI. Patients and tumor characteristics are reported in Table 1. Median age was 81.7 years [range: 58–89]. According to the APBI GEC-ESTRO recommendations, 72.5%, 11.9% and 15.6% were classified as low-, intermediate- and high-risk respectively. The histological type was mainly invasive ductal carcinoma (87.1%). The median tumor size was 10 mm [range: 1–35]. All margins were cleared. All the tumors but 11 had positive hormonal receptor status while Her-2 status was over-expressed in 9 patients (8.1%). According to the molecular classification, 65.1%, 18.3%, 4.6%, 1.8%, 2.8% and 7.4% were classified as Luminal A, Luminal B, Luminal B Her2+, Her2+ (HR-) and Triple Negative respectively.

Table 1  
Patient and tumor characteristics

Characteristics	n	% / range
Median age (year)	81.7	[58–89]
Tumor side		
Left	62	56.9
Right	47	43.1
Median tumor size (mm)	10	[1–35]
pN category		
pN0	97	89
pN1-2	8	7.3
pNx	4	3.7
Histological subtype		
IDC	95	87.1
ILC	6	5.5
OIC	4	3.7
DCIS	4	3.7
Histological grade		
1	44	40.4
2	46	42.2
3	16	14.7
unknown	3	2.7
Hormonal receptor status		
Positive	98	89.9
Negative (OR-/PR-)	11	10.1
Her2 status		
Over-expressed	9	8.2
Non-over-expressed	96	88.1

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, OIC: Other invasive carcinoma, DCIS: ductal carcinoma in situ; LVI: Lympho-vascular invasion

Characteristics	n	% / range
Unknown	4	3.7
LVI		
Yes	2	1.8
No	60	55.1
Unknown	47	43.1
Median Ki67 (%)	10	[5–80]
APBI GEC-ESTRO risk groups		
Low	79	72.5
Intermediate	13	11.9
High	17	15.6
Molecular classification groups		
Luminal A	71	65.1
Luminal B Her2-	20	18.3
Luminal B Her2+	5	4.6
Her 2+ (HR-)	2	1.8
Triple negative	3	2.8
Unknown	8	7.4
Time Interval surgery/APBI (days)	12	[1–105]
Total dose (Gy)	34	[30–35]
Median Number of fractions	10	[5–10]
Median Number of needles	10	[5–24]
Median Number of planes	2	[1–5]
Endocrine therapy		
Yes	94	86.2
No	15	13.8
Chemotherapy		

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, OIC: Other invasive carcinoma, DCIS: ductal carcinoma in situ; LVI: Lympho-vascular invasion

Characteristics	n	% / range
Yes	3	2.7
No	106	97.3
Trastuzumab		
Yes	2	1.8
No	107	98.2
IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, OIC: Other invasive carcinoma, DCIS: ductal carcinoma in situ; LVI: Lympho-vascular invasion		

## Treatment characteristics

The median time interval between surgery and APBI was 12 days [range: 1–105]. A median number of 10 vectors [range: 5–24] on 2 planes [range: 1–5] were implanted. Median total dose was 34 Gy [range: 30–35] for a median number of fractions of 10 [range: 5–10]. The median CTV was 57 cc [range: 11–210]. The median V100% was 96% [range: 69–100] while median Dose Homogeneity Index was 0.61 [range: 0.19–0.81].

Among the 98 patients who were eligible for endocrine therapy, 5 patients refused and 12 patients stopped the treatment prematurely due to poor tolerance. These 12 patients (12.2%) took endocrine therapy for an average of 22 months.

## Oncological outcome

With a median follow-up of 97 months [range: 7–159], 2 (1.8%) local relapses occurred and 2 patients (1.8%) developed an axillary relapse. Eight-year LRFS, MFS, SS and OS were 96.7% [95% CI: 0.923–1], 96.7% [95% CI: 0.924–1], 95.7% [95% CI: 0.910–1] and 71.8% [95% CI: 0.616–0.837] respectively (Fig. 1). Two patients (1.8%) died from cancer with metastatic disease (1 pt in the APBI low-risk group, 1 pt in the high-risk group). Twenty-nine patients (26.6%) died from other causes. Characteristics of the patients who presented disease progression are detailed in Table 2.

Table 2  
 Characteristics of patients who experienced oncological event

Pt#	Age at surgery (years)	TTP (months)	APBI GEC-ESTRO risk	Molecular classification	Histologic features	Oncological event	Status
1	83.6	27.3	High	Triple negative	IDC	Synchronous	Death
					27 mm	regional and	related to
					pN1	metastatic	cancer
					Grade 3		
					HR-		
					Her2-		
					Ki67 50%		
2	79.2	32.9	Low	Luminal B Her2-	IDC	Local	Death
					19 mm	Regional	related to
					pN0	Metastatic	cancer
					Grade 2		
					ER + PR-		
					Her2-		
					Ki67 40%		
3	73.8	63.1	Low	Luminal B Her2-	IDC	Metastatic	Alive
					18 mm		
					pN0		
					Grade 1		
					ER + PR-		
					Her2-		
					Ki67 20%		
4	78.9	86	Intermediate	Unknown	DCIS	Local	Death

IDC: invasive ductal carcinoma; TTP: time to progression; V100: part of the CTV receiving 100% of the prescribed dose;

Pt#	Age at surgery (years)	TTP (months)	APBI GEC-ESTRO risk	Molecular classification	Histologic features	Oncological event	Status
					20 mm		related to
					pN0		other cause
IDC: invasive ductal carcinoma; TTP: time to progression; V100: part of the CTV receiving 100% of the prescribed dose;							

In order to find significant independent prognostic factors for disease progression at 8 years, different variables were analyzed in univariate analysis: age, tumor size, nodal status, histological subtype, histological grade, lympho-vascular invasion, Ki67, HR status, Her2 status, APBI and molecular classifications. In univariate analysis, molecular classification was the only significant prognostic factors. Molecular classification was considered as a significant prognostic factor for OS ( $p < 0.0001$ ), SS ( $p = 0.007$ ) and MFS ( $p = 0.009$ ) but not for LRFS ( $p = 0.586$ ). APBI classification was not considered as prognostic factors for any items: OS ( $p = 0.408$ ), SS ( $p = 0.436$ ), MFS ( $p = 0.616$ ) and LRFS ( $p = 0.406$ ) (Table 3).

Table 3  
Oncological outcome according to APBI and molecular classifications

8-year	APBI classification				Molecular classification				
	LR	IR	HR	p value	Lum. A	Lum. B	Lum. B Her2+	TN	p value
LRFS	98.2	85.7	100	0.328	100	94.4	100	100	0.586
MFS	95.8	100	90.9	0.457	100	87.2	100	66.7	0.009
SS	97.7	100	88.9	0.249	100	92.9	100	66.7	0.007
OS	74.6	88.9	43.5	0.108	72.1	77.9	100	33.3	< 0.0001
LR: Low risk, IR: Intermediate risk, HR: High risk. The 8-year oncological outcomes for the two Her2+ patients are not reported because they do not have sufficient follow-up at the time of the analysis (20 and 23 months respectively)									

## Toxicity profile

Among the 109 patients, at the last follow-up, the maximum complication rate observed after APBI was 88.4% (61 patients) and 11.6% (8 patients) for grades 1 and 2 respectively. No grade  $\geq 3$  was observed. The observed complications consisted mainly in breast fibrosis (60.8%), while telangiectasia (17.4%), hyper-pigmentation (7.2%), deformation (8.7%) and pain (5.8%) were less frequent.

Regarding cosmetic outcome, the rates of excellent and good cosmetic outcomes were 57.8% and 38.6% respectively, while a fair result was observed for 2 patients (1.8%). There was no poor cosmetic outcome

(Table 4).

Table 4  
Late toxicities and cosmetic outcome

<b>Late Toxicity</b>	<b>Number of events</b>	<b>%</b>
Grade 1		
Breast fibrosis	36	33.0
Telangiectasia	10	9.2
Hyperpigmentation	5	4.6
Deformation	6	5.5
Pain	4	3.7
Grade 2		
Fibrosis	6	5.5
Telangiectasia	2	1.8
Cosmetic outcome		
Excellent	63	57.8
Good	42	38.6
Fair	2	1.8
Poor	0	0
Not reported	2	1.8
<b>A B</b>		

## Discussion

Breast conserving treatment is the standard of care for early stage breast cancer (26). RT is a mainstay of this conserving approach, not only allowing a threefold reduction in LR but also improving OS (3,27). Patients aged 70 years and over, who are in good health condition, have a median life expectancy about 15 years and half of them will live much longer.

Elderly breast cancer represents a public health challenge, which will become more and more critical with the upcoming increasing life expectancy during the next decades and the impact of a potential acceptance of breast cancer screening for patients older than 75. For elderly patients presenting with early breast cancer, choosing the appropriate adjuvant treatment remains difficult, and we need to promote more accurate strategies taking into account oncological outcome and treatment toxicity as well as quality of life and health care expenditure.

In order to find an acceptable compromise between no breast irradiation, as suggested in randomized trials (7–12), and 3–5 weeks of WBI, the concept of APBI emerged and has been presented as a good option specifically for the elderly population with breast cancer at low-risk of LR (17,18). The rationale for investigating partial-breast radiotherapy is based on the fact that after breast-conserving surgery, most LR occur at or near the primary site of the cancer (tumor bed) (28,29). Indeed, irradiation is limited to the higher risk area of LR. By increasing the radiation fraction size and decreasing the target volume and consequently decreasing the volume of irradiated normal tissue, APBI represents an alternative for the local treatment of breast cancer, and our extended follow-up enables us to look at the long-term impact of this approach.

Many techniques of APBI have been developed: HIBT, external breast RT and intraoperative radiation therapy. HIBT is one of the first APBI technique used and has the longest follow-up (30,31). The two last trials which reported the comparison between external partial breast RT to WBI confirmed the non-inferiority of the APBI technique in the RAPID trial, (but with a significant deleterious impact in terms of cosmetic outcome) (32,33) but not in the NSABP B-39/RTOG 0413 trial (34). Two trials of intraoperative radiotherapy reported higher rates of LR compared with conventional WBI (35,36). The GEC-ESTRO APBI phase III compared WBI versus APBI for selected primary early-stage breast cancer (low and intermediate-risk groups) (37) and the 5-year LRFs was 98.6%, which is similar to our 5-year LRFs of 98.1% previously described (19). With a 12-year median follow-up, Polgar et al. (38) reported a 5-year LR rate of 4.7% with 77% of good/excellent cosmetic results.

This update confirms the outcome of our cohort while HIBT remains as an attractive technical option (19). In our study, regarding the oncological outcomes of the whole cohort and taking into account that in specific circumstances, we were led to propose APBI even for patients belonging to the APBI GEC-ESTRO high-risk group, the 8-year LRFs, MFS, SS and OS rates were 96.7%, 95.7%, 96.7% and 71.8%, respectively. Focusing on local control, Polgar et al. reported a 10-year LR rate of 9.3% but in a lower risk breast cancer population and younger cohort (median age: 56 years) (38). Our results lead to consider that, in an elderly population presenting with an early breast cancer, APBI could be reasonably proposed for intermediate and even high-risk patients in order to achieve optimal local control rate. Comparing with external beam APBI phase III randomized trials, we observed similar results in terms of local control. With a median follow-up of 10.2 years, the NSABP B-39/RTOG 0413 (34) reported a LRFs rate of 95.4%. With a similar 8-year median follow-up, the LRFs rate reported in the RAPID trial was 97% (32).

In our cohort, we observed that the majority of the patients died from other causes than cancer (Fig. 2). The difference between 8-year SS (96.7%) and OS (71.8%), can mainly be explained by our very old population (median age: 81.7 years) in which a lot of competing mortality factors come into play.

Regarding oncological prognostic factors, according to the GEC-ESTRO APBI classification, we reported 8-year LRFs rates of 98%, 87.5% and 100% for low-, intermediate- and high-risk groups respectively. In univariate analysis GEC-ESTRO APBI classification was not significant for LRFs ( $p = 0.406$ ), MFS ( $p = 0.616$ ), SS ( $p = 0.436$ ) and OS ( $p = 0.408$ ). Although based on a small number of events, it seems that for

elderly patients this classification may not be as accurate as for the younger ones, and APBI could be discussed as a treatment option for selected high-risk patients. In our study, even if the molecular classification (39) was considered as a significant prognostic factor for OS ( $p < 0.0001$ ), SS ( $p = 0.007$ ) and MFS ( $p = 0.009$ ) but not for LRFS ( $p = 0.586$ ), those results must be considered with caution because of the very low number of triple negative patients associated with a related high rate of oncological events (40,41). Nevertheless, molecular classification could impact on local control and has not been considered directly in the GEC-ESTRO APBI classification. Although this classification takes into account HR status, Her2 status and Ki67 are not considered. Considering molecular classification combined with GEC-ESTRO APBI classification could likely lead to a more accurate patient selection for APBI.

In our study, the maximum complication rate observed after APBI, was 88.4% (61 patients), 11.6% (8 patients), grades 1 and 2 respectively. No grade  $\geq 3$  was observed. Other trials evaluating different partial breast irradiation methods have reported good toxicity profile but more grade  $\geq 2$ . The RAPID trial (32) reported 32% of grade  $\geq 2$  and 4.5% of grade 3 while the GEC-ESTRO trial (42) reported 23.3% of cumulative incidence of grade 2 or worse late toxicity. In the NSABP B-39/RTOG 0413 (34) adverse events were worst with a highest toxicity grade reported from APBI of grade 1 in 40%, grade 2 in 44%, and grade 3 in 10%. Regarding cosmetic outcome, the rates of excellent and good cosmetic outcomes were 57.8% and 38.6% respectively, while a fair result was observed for 2 patients (1.8%).

In phase III randomized trials comparing surgery plus endocrine therapy with or without adjuvant WBI, a significant over-risk of LR without breast irradiation was reported (9,11). Due to the deleterious impact of aromatase inhibitors on the quality of life (43), it is currently discussed to promote adjuvant breast irradiation without endocrine therapy in the elderly with low-risk breast cancer (44,45). In our population study, 5 patients refused and 12 patients stopped the treatment prematurely due to poor tolerance. For selected patients, APBI could also be considered as a viable alternative to the omission of adjuvant RT which has been considered for elderly patients, as it drastically reduces the number of transportations, alleviates the treatment related constraints, in particular for elderly patients with frequent comorbidities, without compromising local control. Currently, some protocols want to get further proposing single-fraction HIBT with promising results (46,47).

In a time of cost saving for patients and health care systems, Shah et al. (48) showed in a cost-efficacy study that compared with WBI using three dimensional conformal RT and intensity-modulated RT, every APBI techniques allow for 1000 treated patients, cost savings between \$0.7 and \$6 million and between \$5 and \$14.9 million, respectively. Lanni et al. (49) confirmed that APBI using brachytherapy techniques was less costly than conventional WBI with a standard boost.

The limitations of the present study are mainly represented by its retrospective status, the small number of patients and (fortunately) the very few numbers of oncological events that did not allow performing an accurate statistical analysis for prognostic factors.

## Conclusion

Long-term follow-up confirms that HIBT is safe and effective in an elderly patient cohort of early breast cancer. APBI using HIBT represents a smart alternative between no post-operative irradiation (endocrine therapy alone) and WBI. Our results suggest that selected elderly women presenting with high-risk breast cancer could also be considered for APBI.

In the frame of aging population with an increased breast cancer incidence, healthcare providers, insurers, and administration have to be aware of this issue, to provide to elderly women with early breast cancer, the best therapeutic option combining optimal local control and good quality of life in a cost-effective way.

## Abbreviations

- APBI: Accelerated Partial Breast Irradiation
- CTV: Clinical Target Volume
- HIBT: High-dose-rate Interstitial multicatheter Brachytherapy
- HR: Hormonal Receptor
- LR: Local Recurrence
- LRFS: Local Recurrence Free Survival
- MFS: Metastatic Free Survival
- OS: Overall Survival
- RT: Radiation Therapy
- SS: Specific Survival
- WBI: Whole Breast Irradiation

## Declarations

### Ethics approval and consent to participate

- This study was approved by the Institutional Review Board of Antoine Lacassagne Cancer Centre (n°17013) which approved the ethical aspect of the protocol.
- A statement on ethics approval and consent was provided by the Breast Cancer Research Board of the Antoine Lacassagne Cancer Center.

### Consent for publication

- Consent for publication was obtained from the patients.

### Availability of data and materials

- The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

- The authors declare that they have no competing interests

## Funding

- No

## Authors' contributions

- SS: acquisition of data and analysis, manuscript writing and final approval,
- MP: acquisition of data and analysis and final approval
- JG: statistical analysis and final approval,
- DLCK: data analysis and final approval,
- MG: data analysis and final approval,
- RS: statistical analysis and final approval,
- MEC: data analysis and final approval,
- JMHL: Study concept, design, acquisition of data and analysis, manuscript writing and final approval.

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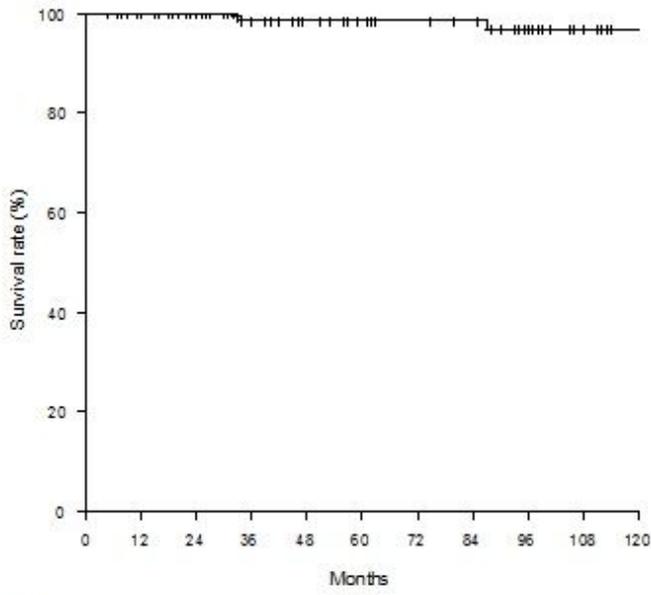
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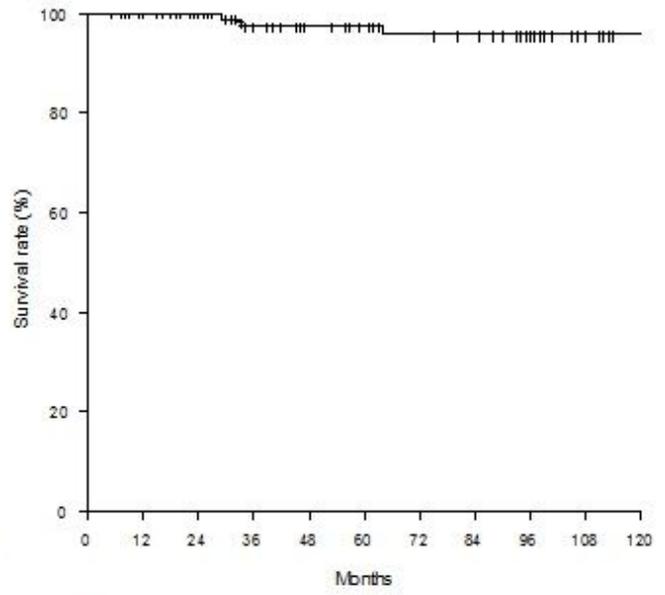
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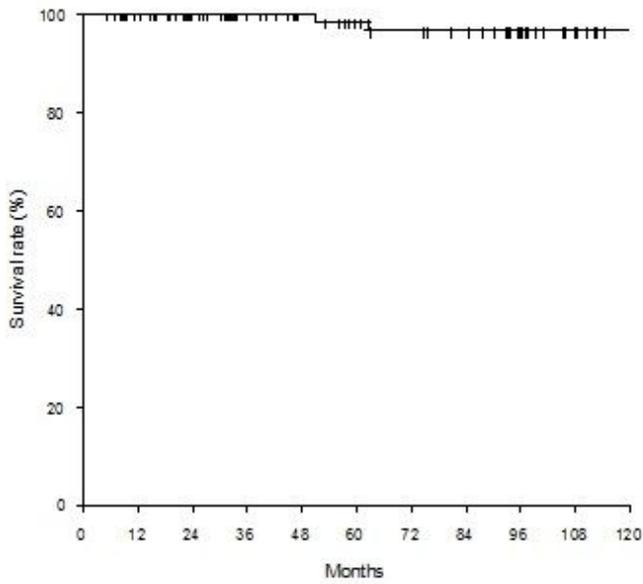
## Figures



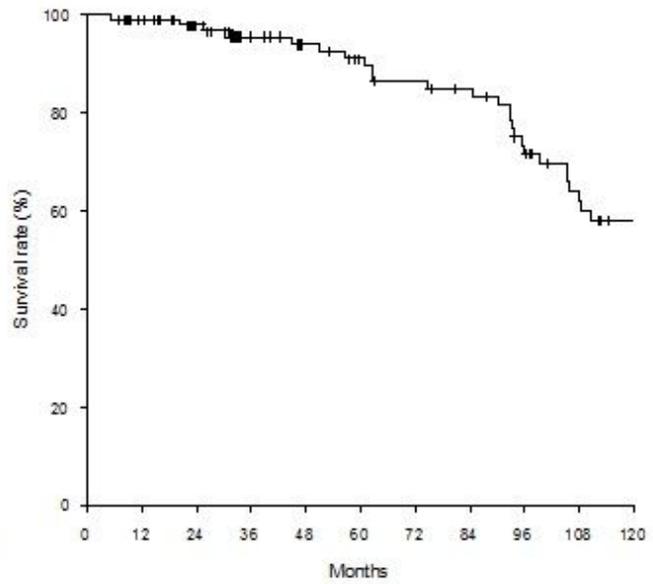
**A**



**B**



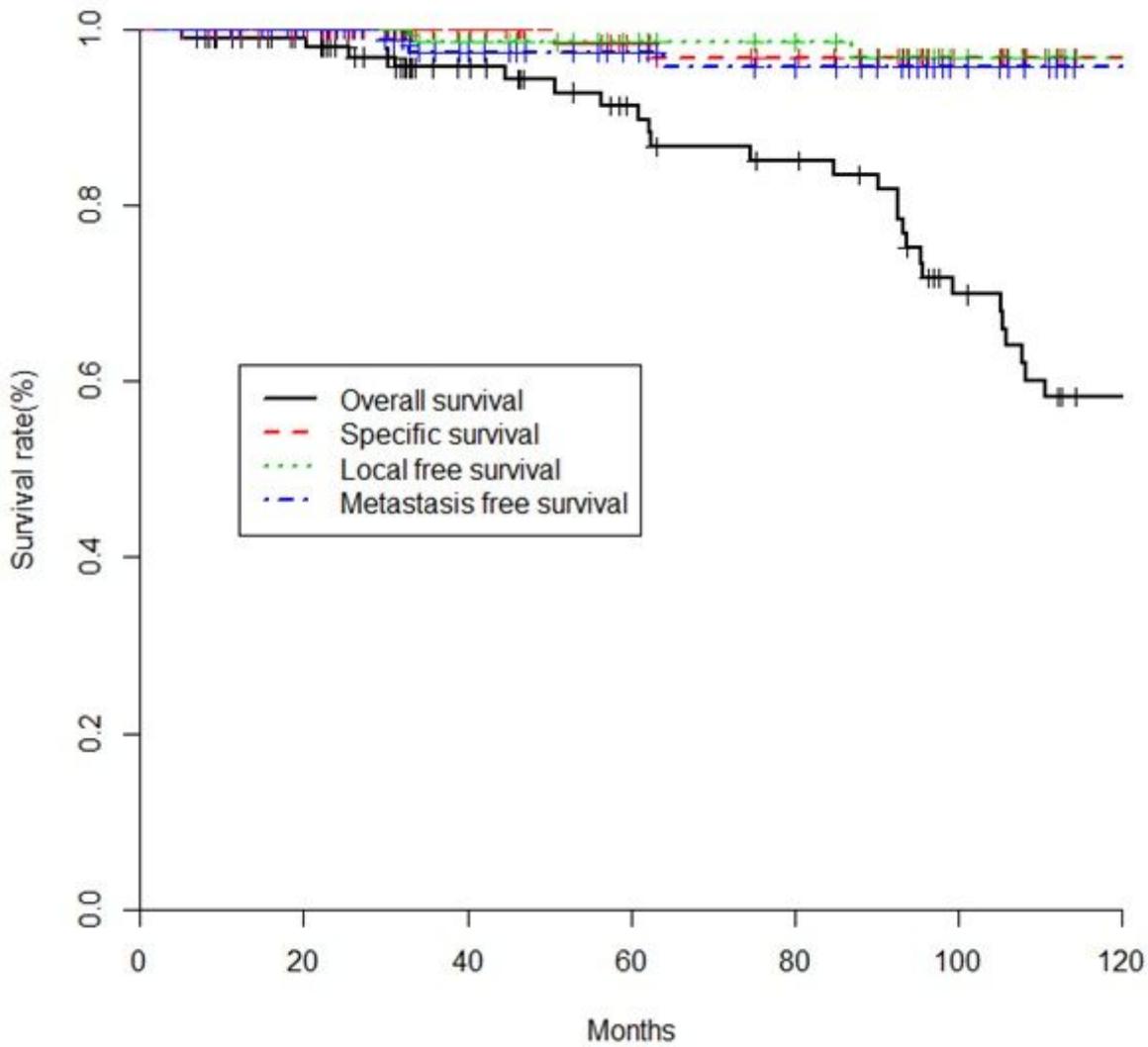
**C**



**D**

**Figure 1**

Local recurrence-free survival (A); Metastatic disease-free survival (B); Specific survival (C); Overall survival (D).



**Figure 2**

Superimposed overall, specific, local-free and metastatic-free survival curves showing the impact of competing factors for overall survival in the elderly.