

Intraoperative Radiotherapy with INTRABEAM® in Early-Stage breast Cancer patients: a 10-Year Monocentric experience

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Abstract

Purpose

Whole-breast irradiation (WBI) after breast-conserving surgery (BCS) may be challenging in older patients due to comorbidities and logistical constraints. Intraoperative radiotherapy (IORT) represents an attractive ultra-short alternative. This study reports a 10-year retrospective monocentric experience using INTRABEAM® in early-stage breast cancer (BC) patients.

Methods

A retrospective cohort study was conducted including 247 consecutive patients treated with IORT using INTRABEAM® as initial treatment between 2012 and 2021 at a single comprehensive cancer center. Eligible patients had a histologically confirmed BC and underwent BCS with IORT. Clinical, pathological, treatment-related, and outcome data were retrospectively analyzed.

Results

The median age was 71.6 years, with 61.5% of patients aged ≥ 70 years. Tumors were predominantly ≤ 20 mm (94.3%), hormone receptor–positive (95.1%), HER2-negative (96%), and of low to intermediate histological grade. Postoperative grade II complications occurred in 13% of patients, mainly seromas requiring aspiration (12.1%) and infections requiring antibiotic therapy (0.8%). Additional WBI was required in 20.6% of patients. After a median follow-up of 50.4 months (95% CI: 47.7–56.1), the 5-year LR rate was 1.2%. Survival analyses, restricted to patients treated with IORT alone, showed 5-year disease-free survival and overall survival rates of 85.5% and 91.8%, respectively.

Conclusion

Single-session IORT delivered during BCS provides favorable long-term oncological outcomes with acceptable toxicity in selected early-stage BC patients. This approach represents a convenient and well-tolerated alternative to conventional WBI, particularly for elderly or frail populations.

Introduction

In 2022, more than two million patients were diagnosed as having breast cancer (BC) worldwide and 665,000 patients died from the disease (1). For patients with early-stage disease, breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT) has been established as the standard of care, providing local control (LC) and overall survival (OS) outcomes equivalent to mastectomy (2–4). Evidence from randomized trials indicates that whole-breast irradiation (WBI) following BCS results in a

15.7% absolute reduction in the 10-year risk of first recurrence and a 3.8% reduction in breast cancer-specific mortality at 15 years (5).

Despite its proven efficacy, conventional WBI requires several weeks of daily treatment and may be associated with acute and late toxicities, including fibrosis, edema, and irradiation of surrounding organs such as the heart and lungs (6, 7). These limitations may complicate access to standard RT in routine practice and negatively impact treatment adherence and quality of life, particularly in frail or comorbid patients (8).

To address these limitations, partial breast irradiation (PBI) has been developed as an alternative approach for selected patients with low-risk early-stage BC. The rationale for PBI is based on the consistent spatial pattern of local relapse, with majority of recurrences occurring close to the primary tumor bed. Retrospective and prospective studies, including randomized clinical trials, have demonstrated that over 90% of LR arise within the index quadrant, supporting the use of targeted irradiation approaches. Several techniques have been investigated, including brachytherapy (9), external beam accelerated partial breast irradiation (APBI) (10, 11), and intraoperative radiotherapy (IORT) (12, 13), with the aim of reducing irradiated volumes while maintaining adequate oncological control.

IORT delivers a single fraction of radiation directly to the tumor bed at the time of BCS, allowing precise targeting of tissues at highest risk while sparing surrounding healthy structures. The INTRABEAM® system, which uses low-energy X-rays with a rapid dose fall-off, has been widely studied and offers favorable dosimetric and logistical properties. By completing surgery and RT in a single procedure, IORT substantially shortens overall treatment time and may improve patient convenience and quality of life (14). Although early randomized trial results initially limited widespread adoption, contemporary trends toward hypofractionated (15–17) and ultra-hypofractionated RT (18) schedules have renewed interest in highly condensed treatment strategies such as IORT.

In this context, long-term real-world data are needed to better define the role of IORT in routine clinical practice. This study reports a 10-year retrospective monocentric experience evaluating INTRABEAM®-based IORT as initial treatment in early-stage BC, focusing on patient and tumor characteristics, treatment-related toxicity, and oncological outcomes

Materials and Methods

Patient selection

Between January 2012 and December 2021, all patients with histologically confirmed early BC were consecutively treated with BCS followed by IORT at our institution. Since IORT is not considered as a standard of care but rather as an alternative approach, each indication for BCS with IORT was reviewed and approved by a multidisciplinary tumor board. Eligible patients were selected based on predefined inclusion criteria. IORT was offered either within the framework of prospective clinical trials (TARGIT-A, TARGIT-B, TARGIT-E, RIOP, or RE IORT 01) or, outside clinical studies, according to the eligibility

recommendations of the American Society for Radiation Oncology (ASTRO) guidelines in effect at the time of treatment (19). Preoperative mammography and ultrasound were systematically performed to determine lesion size. Magnetic resonance imaging (MRI) could be used to complement the assessment, when necessary, at the discretion of the radiologist or surgeon. Only patients treated exclusively with IORT using the Intrabeam® system were included in the survival analyses; those requiring additional local treatment (e.g., re-excision for positive margins) were excluded.

Details regarding the patient, tumor characteristics, surgical procedures, and outcomes were collected from medical records. Following the process of anonymization, this information was entered into a REDCAP database. Each patient was given information about IORT and standard adjuvant RT. This study was approved by the local Ethical Committee.

Treatment characteristics

IORT was delivered using the INTRABEAM® system (Carl Zeiss, Oberkochen, Germany), which provides 50 kV X-rays. A unique dose of 20 Gy was prescribed at the applicator surface (according to TARGIT physics group practice), using a low-energy X-ray source emitted from the center of a spherical applicator placed in direct contact with the tumor bed. This device, available in France since 2010, allows precise radiation of the lumpectomy cavity immediately after tumor excision. The procedure required the presence of a surgeon, radiation oncologist, and medical physicist. The applicator size (ranging from 2.5 cm to 5.0 cm in diameter, by 5 mm step) was selected according to the dimensions of the lumpectomy cavity and determined the radiation duration. A purse-string suture was placed to ensure close apposition of the breast tissue to the applicator surface, while the skin was retracted away using a retractor. After completion of IORT, the applicator was removed, meticulous hemostasis was achieved, and standard glandular and skin closure was performed. The tumor bed was not drained. All patients received preoperative antibiotic prophylaxis.

Final pathological results were reviewed in a multidisciplinary tumor board to determine the need for additional surgery or adjuvant therapy according to institutional guidelines. Complementary WBI and/or re-excision were recommended when criteria for IORT alone were not fulfilled. IORT was considered to provide the tumor bed boost; therefore, no additional external-beam boost was delivered. RT could be omitted in selected cases due to significant comorbidities or patient refusal.

Adjuvant WBI was recommended in the presence of high-risk pathological features, including tumor size > 2 cm, positive margins, extensive intraductal component, invasive lobular histology, multifocal or multicentric disease, lymphovascular invasion (LVI), nodal involvement, SBR grade III, hormone receptor negativity, or HER2 overexpression, in accordance with ASTRO APBI guidelines (19).

R0 resection was defined as no ink on tumor for invasive carcinoma and ≥ 2 mm margins for DCIS. R1 status prompted re-excision followed by WBI. Additional axillary surgery was performed when ≥ 3

sentinel nodes were positive or in cases of macroscopic extracapsular extension, according to ACOSOG Z0011 criteria (20).

Systemic adjuvant therapy was administered as per standard practice

Follow-up

Postoperative complications were prospectively evaluated during follow-up and graded according to the Clavien–Dindo classification by the treating surgeon or radiation oncologist. Complications occurring beyond one year after surgery were considered late events and were classified using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical analysis

Ipsilateral breast tumor recurrence (IBTR) was defined as any new invasive or in situ carcinoma occurring in the treated breast. Disease-free survival (DFS) was calculated from the date of surgery to the occurrence of local, regional, contralateral, or distant recurrence, second primary cancer, or death from any cause, whichever occurred first. OS was defined as the time from surgery to death from any cause.

Time to local recurrence (LR) was defined as the interval between surgery and ipsilateral breast and/or axillary recurrence. Other recurrences, second primary cancers, or death were treated as competing events. Cumulative incidence of LR was estimated using the Aalen–Johansen method to account for competing risks, and 5-year cumulative incidence rates were reported with 95% confidence intervals.

OS and DFS were estimated using the Kaplan–Meier method, with 5-year survival rates presented with 95% confidence intervals. Median follow-up was calculated using the reverse Kaplan–Meier method. Patients without events were censored at the date of last follow-up. Complication rates were expressed as proportions of patients experiencing at least one event, with 95% confidence intervals.

Data collection was managed using REDCap (version 9.1.3, Vanderbilt University), and statistical analyses were conducted using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Between January 2012 and December 2021, 247 patients were consecutively treated with BCS followed by IORT using the Intrabeam® device for early-stage BC at our institution.

The median age was 71.6 years. Most patients had a BMI <30 kg/m² (76.1%) and were classified as ASA II (65.6%). Tumor laterality was balanced between the right (46.6%) and left breast (53.4%).

Tumors were predominantly small, with 94.3% measuring ≤ 20 mm. Nodal status was negative in 86.8% of cases. Histologically, most tumors were invasive ductal carcinoma associated with ductal carcinoma in situ (56.3%) or invasive ductal carcinoma alone (31.2%).

Hormone receptor positivity was frequent (ER 95.1%, PR 78.9%), while HER2 overexpression and triple-negative subtype were uncommon (4.0% and 2.0%, respectively). Most tumors were grade I–II (89.4%), LVI was observed in 9.3% of cases, and surgical margins were negative (R0) in 94.7% of patients. Patient and tumor characteristics are summarized in **Table 1**.

No patients received neoadjuvant chemotherapy. Neoadjuvant endocrine therapy was administered in 16 patients (6.5%), mainly to delay surgery during the COVID-19 pandemic, and in rare cases due to initial refusal of surgery or to downstage the tumor before BCS.

Treatment

For IORT, the duration of irradiation depended on the applicator size, with a median irradiation time of 25.0 minutes (range, 18–50). The median applicator diameter was 3.5 cm (range, 2.5–5 cm).

Among the 247 patients treated with IORT as initial treatment, 22 (8.9%) did not receive any adjuvant therapy. WBI was administered in 51 patients (20.6%), re-excision was performed in 9 patients (3.6%), and adjuvant chemotherapy was given to 15 patients (6.1%). Endocrine therapy was prescribed in most patients (213; 86.2%), and among those who received endocrine therapy, 84.9% were treated for at least 5 years.

Endocrine therapy alone was the most frequent treatment regimen (68.4%). Other combinations included WBI plus endocrine therapy (11.3%), WBI with chemotherapy and endocrine therapy (2.8%), and WBI with chemotherapy (1.6%). Re-excision combined with adjuvant treatments was uncommon. Details of adjuvant treatments are summarized in **Table 2**.

Toxicities

Most patients did not experience postoperative complications (71.3%), while 20.2% had one complication and 8.5% had two or more. Postoperative infections occurred in 10.1% of patients (9.3% grade I, 0.8% grade II). Seroma was observed in 17.3% of cases, including 12.1% requiring aspiration. Delayed wound healing occurred in 10.1% of patients, and surgical reintervention was rare (0.8%).

Late complications were uncommon, with 73.7% of patients reporting none. Fat necrosis was the most frequent late event (21.4%), mainly grade I. Pain occurred in 7.7% of patients, while radioepidermitis was rare (1.2%). A second surgical intervention related to late complications was required in one patient (0.4%). These complications are summarized in **Table 3**.

Patient outcomes

Among the 247 patients initially treated with IORT, the median follow-up was 51.7 months (95% CI: 48.3–56.5; 4.3 years). During follow-up, 3 patients (1.2%) developed an IBTR, 4 patients (1.6%) experienced a contralateral recurrence (breast or axillary), and 4 patients (1.6%) developed distant metastases. The clinical and pathological characteristics of patients who developed recurrences are presented in **Table 4**. The most frequent histology among IBTR cases was invasive ductal carcinoma, with a mean time to IBTR of 6.6 years. One patient presented multiple sites of recurrence, including both ipsilateral and contralateral disease.

Overall, 16 patients (5.6%) died during follow-up; only one death was related to BC, while the cause of death was unknown in four cases. Three patients (1.0%) were lost to follow-up.

Survival analyses were restricted to patients treated with INTRABEAM® alone (n = 187). The 5-year DFS was 85.5% (95% CI: 77.9–90.6): 8 patients (4.3%) died, 6 (3.2%) experienced recurrence, and 12 (6.4%) developed a second cancer (**Fig. 1**). The 5-year OS rate was 91.8% (95% CI: 84.5–95.8) (**Fig. 2**).

Discussion

In the present retrospective monocentric study, IORT delivered with the INTRABEAM® system as initial treatment was associated with excellent LC and favorable survival outcomes in a carefully selected population of patients with low-risk early-stage BC. The observed 5-year IBTR rate of 1.2% is consistent with the results of the TARGIT-A trial, which reported a 5-year LR rate of 2.11% in the risk-adapted IORT arm (13). Our findings also compare favorably with those of the ELIOT trial, which reported a 5-year recurrence rate of approximately 4.4% in the IORT arm and higher long-term recurrence rates reaching 12.6% at 15 years (12, 21). These differences likely reflect variations in patient selection as well as differences in radiation technique, with ELIOT using electron-based IORT whereas TARGIT-based approaches rely on low-kV photons delivered with the INTRABEAM® system.

In this cohort, 20.6% of patients required complementary WBI following final pathological analysis. This rate is comparable to that reported in the risk-adapted strategy of the TARGIT-A trial, highlighting the importance of appropriate preoperative patient selection to minimize the need for additional postoperative RT (13).

In the present study, the toxicity profile observed was acceptable, with most adverse events being low-grade complications such as seroma and fat necrosis. The seroma rate of 17.3% in this cohort and is consistent with previously reported rates following IORT, generally ranging between 11% and 20% in the literature (22–25). Delayed complications such as persistent pain or fat necrosis were relatively uncommon and appeared less frequent than those reported by Key et al. (26). These findings are consistent with the safety profile reported in large prospective trials of IORT. In the TARGIT-A trial, rates of severe radiation-related toxicity were low and comparable to those observed after WBI (27). Cosmetic outcomes following IORT have also been reported as favorable, with good or excellent cosmetic results observed in approximately 85–90% of patients in most published series (28, 29). Overall, our findings support the favorable tolerability of IORT when used in appropriately selected patients

Appropriate patient selection is a key determinant of oncological outcomes when IORT is used as the sole adjuvant irradiation. International guidelines from the American Society for Radiation Oncology (ASTRO) and the ESTRO/ACROP consensus recommend APBI for carefully selected patients presenting with low-risk features, typically including age ≥ 50 –60 years, tumor size ≤ 2 –3 cm, node-negative disease, negative surgical margins, hormone receptor–positive tumors, and absence of LVI or extensive intraductal component (30, 31). These criteria closely match the characteristics of our cohort, which consisted predominantly of small, hormone receptor–positive, HER2-negative tumors with favorable pathological features. Similar selection strategies were applied in major randomized trials evaluating IORT, particularly the TARGIT-A trial, where a risk-adapted approach achieved excellent LC in appropriately selected patients (13). Our findings further emphasize that strict adherence to these selection criteria is essential to maintain low recurrence rates and limit the need for complementary postoperative WBI.

Elderly patients represent a particularly relevant population for treatment de-escalation strategies in early-stage BC, as many present with favorable tumor biology and may experience difficulties completing prolonged RT schedules. In this setting, IORT offers the advantage of delivering adjuvant irradiation during surgery, thereby reducing treatment burden. The prospective TARGIT-E study, which evaluated risk-adapted IORT using the INTRABEAM® system in women aged ≥ 70 years with low-risk BC, reported encouraging outcomes, with a 5-year LR rate of approximately 2.7% and OS exceeding 90%, supporting the feasibility of this approach in carefully selected elderly patients(32). These findings should be interpreted in the context of randomized trials evaluating RT omission in older populations. In CALGB 9343, women aged ≥ 70 years treated with lumpectomy and endocrine therapy had a 10-year LR rate of 2% with RT versus 10% without RT, without any difference in OS (33). Similarly, the PRIME II trial reported 10-year LR rates of 0.9% with RT compared with 9.5% without RT, again with no survival difference (34). Together, these data suggest that while RT omission may be acceptable in selected elderly patients, IORT may represent a pragmatic intermediate strategy that preserves LC while minimizing treatment burden

Recent years have seen increasing efforts toward therapeutic de-escalation in breast RT, aiming to maintain oncological efficacy while reducing treatment burden. Hypofractionated WBI has progressively replaced conventional fractionation following the START trials, which demonstrated equivalent tumor control with shorter schedules (16, 17). More recently, the FAST-Forward trial showed that ultra-hypofractionated RT delivered in five fractions over one week achieved 5-year ipsilateral breast tumor relapse rates of approximately 1.4%, confirming the safety of further treatment shortening (18). In parallel, strategies reducing the irradiated breast volume, such as APBI delivered with brachytherapy or external beam radiotherapy (EBRT), have demonstrated comparable outcomes in selected patients, with 10-year recurrence rates ranging from approximately 2–3.5% in randomized trials (9, 11). Within this evolving landscape of treatment de-escalation, IORT represents the most condensed approach, delivering a single fraction of radiation directly to the tumor bed during surgery while avoiding several weeks of postoperative irradiation.

This study has several limitations inherent to its retrospective and monocentric design. Selection bias may have influenced outcomes, as patients were carefully selected according to institutional criteria. Additionally, the relatively limited follow-up may underestimate late recurrences.

Conclusion

In this retrospective monocentric study, IORT delivered with the INTRABEAM® system during BCS achieved excellent LC with acceptable toxicity in carefully selected patients with low-risk early-stage BC. These results are consistent with previously published randomized trials and support IORT as a feasible single-session alternative to WBI. In the current context of therapeutic de-escalation, this approach represents an attractive option, particularly for elderly or frail patients.

Declarations

Ethics approval: This study was approved by the Ethics Committee of Institut Bergonié (Bordeaux, France).

Consent to participate: Informed non-opposition was obtained from all patients included in the study.

Clinical trial number: not applicable.

Consent for publication: Not applicable

Availability of supporting data: Not applicable

Competing interests : 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.

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Authors' contributions :

- *Concept and design:* A.V., N.M., M.F., C.H.
- *Collection and/or assembly of data:* A.V.,
- *Acquisition, analysis, or interpretation of data:* A.V., C.H., C.B.
- *Drafting of the manuscript:* A.V., C.H.
- *Critical revision of the manuscript for important intellectual content:* C.H., I.T., M.M., J.C., S.A., A.D.L.R., J.B., S.H., N.D., M.F., C.B., A.P., N.M.,
- *Supervision:* C.H., N.M., M.F.

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Tables

Tables 1 to 4 are available in the supplementary files section

Figures

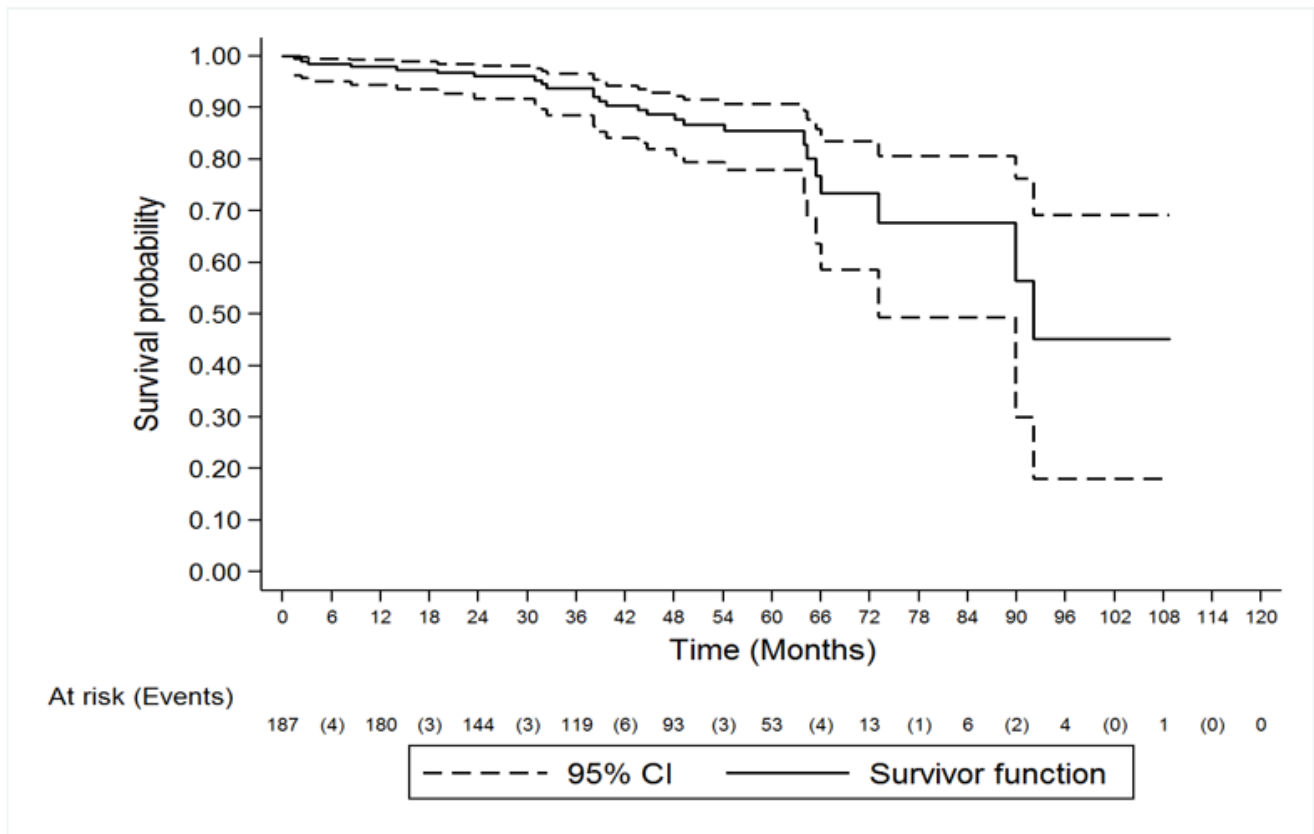


Figure 1

Disease free survival of patients who received IORT only as initial treatment (N=187)

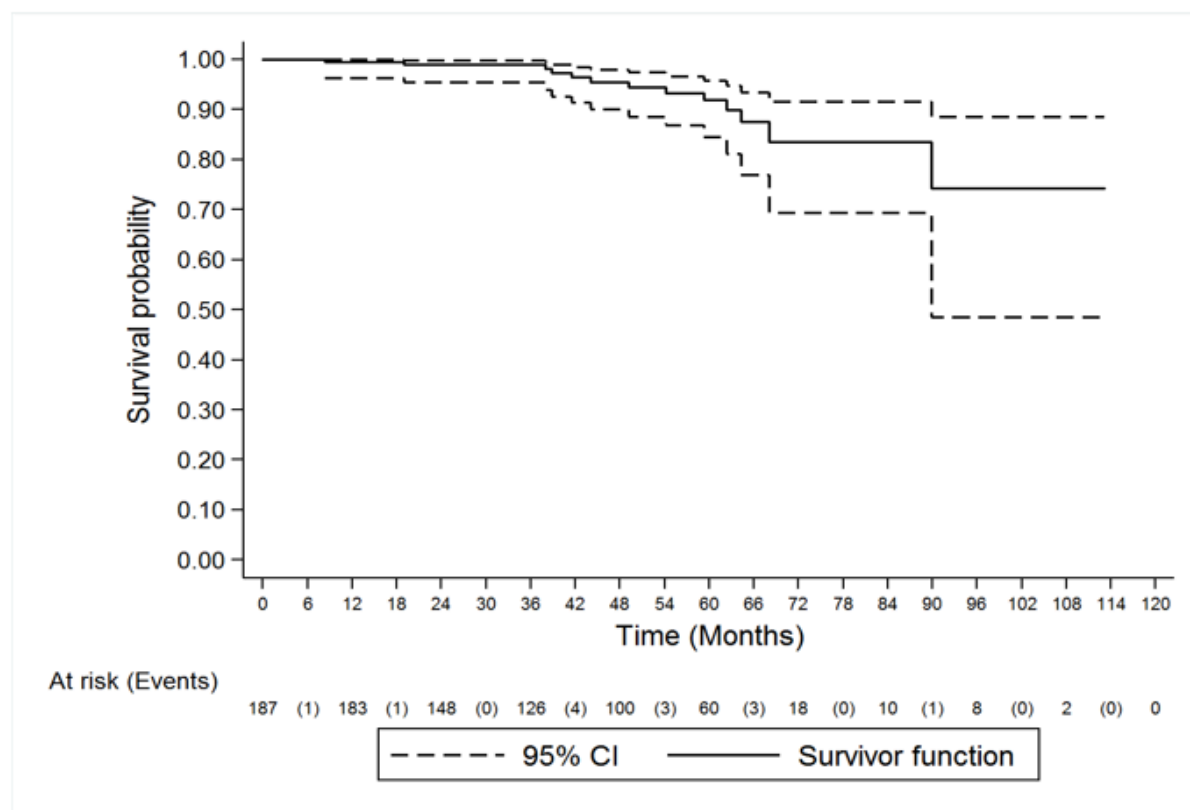


Figure 2

Overall survival of patients who received IORT only as initial treatment (N=187)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)
- [Table2.docx](#)
- [Table3.docx](#)
- [Table4.docx](#)