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Factors Impacting Local Relapse Risk and Disease-Free Survival of Early Breast Cancer receiving Intraoperative Radiation Therapy in Taiwan

Shen-Liang Shih[1,2,3], Jung-Yu Kan[1,3], Hidenobu Takahashi[3], Fan-Ming Chen[1,3], Chieh-Ni Kao[3], Chieh-Han Chuang[4], Chung-Liang Li[1,3], Ping-Fu Yang[1,3], Li-Chun Kao[1], Chia-Yu Kuo[3], Ming-Feng Hou[1-3], Jen-Yang Tang[1-3]

[1] School of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Chung Ho Memorial Hospital
[2] School of Medicine, Kaohsiung Medical University, Taiwan
[3] Department of Breast Surgery, E-DA Kaohsiung Medical Complex Hospital
[4] Department of Radiation Oncology, Kaohsiung Medical University Chung Ho Memorial Hospital, Kaohsiung Medical University

[1] School of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Gangshan Hospital
[2] School of Medicine, Kaohsiung Medical University, Taiwan
[3] Department of Biomedical Science and Environmental Biology, College of Life Science, Kaohsiung Medical University

Abstract

Background: Intraoperative radiation therapy (IORT) delivered during breast-conserving surgery may streamline treatment and enhance cosmetic outcomes. However, optimal patient selection criteria remain uncertain, especially in Asian populations, where international guidelines may not be fully applicable. This study aimed to evaluate local recurrence rates, identify key prognostic factors, and assess the impact of supplemental external beam radiation therapy (EBRT) in Taiwanese patients receiving IORT.

Materials and methods: This retrospective analysis included 1,006 Taiwanese patients who underwent IORT between June 2016 and December 2021. Patients were stratified into low-risk and high-risk groups based on clinicopathological features, including tumor size ≤ 3.5 cm, negative nodal involvement, N+(1-3) tumor size ≤ 3.5 cm, negative nodal involvement, N+(1-3) with micrometastasis, and HR+/HER2- negativity. Patients who did not meet one or more of these criteria were classified as high-risk and were recommended to receive supplemental external beam radiation therapy (EBRT) following IORT.

Results: In our cohort of 1,006 patients, the 6-year disease-free survival rate was 93.11% [95% confidence interval (CI): 91.6–94.4%], with 87 patients (8.99%) experiencing recurrence. The median age was 52 years, and the median follow-up duration was 30.5 months. The overall local recurrence rate was 8.3%, which declined to 1.78% after excluding patients who did not receive indicated adjuvant therapies. Multivariable analysis identified N+(1-3) with micrometastasis, HR+/HER2- negativity, and omission of recommended EBRT as significant predictors of local recurrence, whereas age < 45 was not independently associated with increased risk. Among high-risk patients, the addition of EBRT was associated with a 68.8% reduction in recurrence, achieving outcomes comparable to those of low-risk patients.

Conclusions: Age alone should not determine IORT eligibility. A multifactored approach, including tumor biology and clinicopathological features, is essential. Omitting supplemental EBRT increases recurrence in high-risk patients, and adopting guidelines may enhance patient selection in Asian populations. Keywords: breast cancer; intraoperative radiotherapy; local recurrent risks

Introduction

Breast-conserving surgery (BCS) followed by radiotherapy is the gold standard for early-stage breast cancer, offering survival comparable to mastectomy while preserving breast tissue and achieving favorable cosmetic outcome. Advances in radiotherapy have led to more patient-centered approaches. Intraoperative radiation therapy (IORT), delivering a single high-dose of radiation directly to the tumor bed during surgery, may reduce overall treatment time and limit radiation exposure to healthy tissues. These advantages can improve cosmetic results and quality of life.

Despite IORT's promise, optimal patient selection criteria remain controversial. Traditional guidelines often rely on factors such as age thresholds and tissue risk categories, which may not capture key tumor biology nuances. Additionally, anatomical considerations, including the location of the tumor within the breast and can alter the geometry of the tumor bed, potentially affecting IORT delivery accuracy and efficacy. Moreover, many established international guidelines originate from Western populations and may not fully translate to Asian contexts, where breast cancer often presents at a younger age and may have distinct biological characteristics.

The applicability of standard selection criteria to Taiwanese patients, for instance, requires validation. Recognizing which factors truly predict local recurrence in this population can guide more tailored approaches. Beyond age, variables such as N+(1-3) micrometastasis, and HR/HER2 expression can refine risk stratification. Identifying patients who might benefit from additional therapies, such as external beam radiation therapy (EBRT) after IORT, is crucial. Patients with IORT in high-risk cases may reduce local recurrence and align their outcomes with lower-risk cohorts.

This study evaluates local recurrence rates in a large cohort of Taiwanese breast cancer patients treated with IORT and stratified by guideline-based criteria. By focusing on factors like HR+/HER2- hormone receptor status, and the need for supplemental EBRT, we aim to refine patient selection. We also consider oncoplastic procedures and their impact on local control. The insights gained may inform more personalized guidelines, improving outcomes not only in Taiwan but potentially throughout Asia where similar clinical and biological contexts exist.

Methods and Materials

This study conducted a retrospective cohort study of patients receiving IORT at Kaohsiung Medical University-affiliated hospitals in Taiwan from June 6, 2016, to December 30, 2021. Institutional Review Board approval was obtained (KMUHIRB-E(I)(20210512)). The requirement for informed consent was waived due to the retrospective design and use of anonymized data.

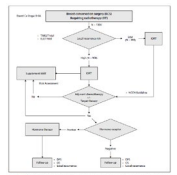


Figure 1. Global workflow of IORT (Intraoperative Radiation Therapy) in breast-conserving surgery. The diagram illustrates the decision-making process for patients undergoing BCS with R0 margins confirmed. Patients are evaluated for eligibility for IORT, with those receiving IORT undergoing local excision (LE) followed by IORT delivery. Post-excision, patients may undergo lumpectomy bed closure or mid-level mammotome placement. Subsequent treatments include chemotherapy, hormone therapy, or mastectomy, depending on tumor characteristics and margin status. Abbreviations: BCS = breast-conserving surgery; IORT = intraoperative radiation therapy; LE = local excision; R0 = negative margins.

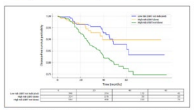


Figure 2. Kaplan-Meier disease-free survival curves and numbers at risk for high-risk patients (+/- supplemental external beam radiation therapy (EBRT)) Vs low-risk patients (+/- supplemental external beam radiation therapy (EBRT)) Vs.

Results

Table 1. Patient demographics and tumor characteristics

Characteristic	Number of patients (%)
Total patients	1006 (100%)
Age (years)	
Median (IQR)	52 (46–59)
Range	20.0 – 91.0
< 40	138 (13.7%)
41–50	411 (40.7%)
51–60	311 (30.8%)
61–70	111 (11.0%)
> 70	39 (3.9%)
Tumor size (cm)	
Median (range)	1.5 (0.1 – 3.5)
≤ 1	397 (39.4%)
1.1–2	424 (42.1%)
2.1–3.5	129 (12.8%)
> 3.5	56 (5.6%)
Histological type	
Invasive ductal carcinoma	912 (90.6%)
DCIS	33 (3.3%)
Invasive lobular carcinoma	21 (2.1%)
Mixed	21 (2.1%)
Other	19 (1.9%)
Tumor grade	
Grade I	119 (11.8%)
Grade II	628 (62.4%)
Grade III	259 (25.7%)
Multifocal	
Multifocal/multicentric	53/953 (5.6%)
Tumor positive	113 (11.2%)

Characteristic	Number of patients (%)
Molecular subtype	
Luminal A	614 (61.1%)
Luminal B	287 (28.5%)
HER2-enriched	49 (4.9%)
Triple-negative	56 (5.6%)
Unknown	0/0 (0%)
Hormone receptor status	
ER+/PR+	859 (85.4%)
ER+/PR-	106 (10.5%)
ER-/PR+	11 (1.1%)
ER-/PR-	30 (3.0%)
HER2 status	
Positive	106 (10.7%)
Negative	1,000 (89.3%)
Unknown	0/0 (0%)
AJCC N stage	
N0	530 (53.0%)
N1	405 (41.1%)
Unknown	0 (0.0%)
Margin status	
Negative (-ink)	1,006 (100.0%)
Close (<2mm)	0/0 (0%)
Unknown	0/0 (0%)
Local/Distant site Recurrence	
Overall	83 (8.2%)
Breast	1,006 (83.2%)
Unknown	0/0 (0%)
Follow-up duration (months)	
Median (range)	30.5 (0.7–71)

IQR = interquartile range; DCIS = ductal carcinoma in situ; HER2 = human epidermal growth factor receptor 2; ER = estrogen receptor; PR = progesterone receptor.

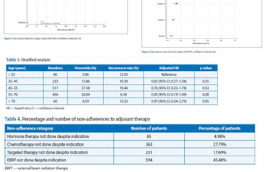


Figure 3. Kaplan-Meier survival curves for overall survival (OS) and disease-free survival (DFS) in patients with and without micrometastasis (N+(1-3) micrometastasis vs. N0). The shaded areas represent 95% confidence intervals. The number at risk is shown below the x-axis.

Table 2. Cox proportional hazard models for overall survival and disease-free survival

Variable	Hazard ratio (95% CI)	p-value
N+(1-3) micrometastasis	2.29 (1.16–4.51)	0.017
Omission of hormone therapy	2.47 (1.49–4.11)	0.000
Omission of supplemental EBRT	4.98 (3.14–8.20)	0.000
Local recurrence (vs. 0%)	0.59 (0.366–1.00)	0.050
Age under 45 years	0.91 (0.57–1.53)	0.746

CI = confidence interval; EBRT = external beam radiation therapy.

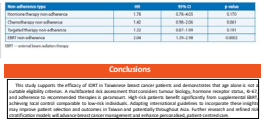


Figure 4. Kaplan-Meier survival curves for overall survival (OS) and disease-free survival (DFS) in patients with and without hormone therapy. The shaded areas represent 95% confidence intervals. The number at risk is shown below the x-axis.

Figure 5. Kaplan-Meier survival curves for overall survival (OS) and disease-free survival (DFS) in patients with and without omission of EBRT. The shaded areas represent 95% confidence intervals. The number at risk is shown below the x-axis.

Table 3. Stratified analysis

Age (years)	Numbers	Percentile (%)	Recurrence rate (%)	Adjusted HR	p-value
< 35	40	3.98	12.50	Reference	
35–40	103	13.86	10.20	0.85 (95% CI: 0.27–3.58)	0.81
41–55	557	27.28	10.48	0.76 (95% CI: 0.31–2.78)	0.52
55–70	406	28.84	6.28	0.45 (95% CI: 0.19–1.09)	0.08
> 70	60	4.59	13.33	0.97 (95% CI: 0.24–2.79)	0.95

HR = hazard ratio; CI = confidence interval.

Table 4. Percentage and number of non-adherences to adjuvant therapy

Non-adherence category	Number of patients	Percentage of patients
Hormone therapy not done despite indication	46	4.58%
Chemotherapy not done despite indication	263	27.79%
Targeted therapy not done despite indication	217	7.59%
EBRT not done despite indication	594	45.48%

EBRT = external beam radiation therapy

Table 5. Impact of hazard ratio (HR), 95% confidence interval (CI) and p-value of non-adherences to adjuvant therapy

Non-adherence type	HR	95% CI	p-value
Hormone therapy non-adherence	1.78	0.76–4.05	0.170
Chemotherapy non-adherence	1.42	0.95–2.06	0.083
Targeted therapy non-adherence	1.32	0.87–1.99	0.191
EBRT non-adherence	2.04	1.39–2.98	0.0002

EBRT = external beam radiation therapy

Conclusions

This study supports the efficacy of IORT in Taiwanese breast cancer patients and demonstrates that age alone is not a suitable eligibility criterion. A multifactored risk assessment that considers tumour biology, hormone receptor status, N+(1-3) and adherence to recommended therapies is paramount. High-risk patients benefit significantly from supplemental EBRT, which can reduce recurrence rates to levels comparable to those of low-risk patients. Omitting this treatment may increase recurrence. Aligning regional patient selection and outcomes in Taiwan and potentially throughout Asia. Further research and refined risk stratification models will advance breast cancer management and enhance personalised, patient-centred care.

Contact
Shen-liang Shih MD, MSc, PhC BSc.
Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Chung Ho Memorial Hospital, Taiwan
Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Gangshan Hospital, Taiwan
School of Medicine, Kaohsiung Medical University, Taiwan
Website: https://orcid.org/0000-0001-8438-5931 Email:shihl1@gmail.com; Phone:886-7-3121101#8235

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