The Breast 77 (2024) 103782

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Postoperative complications of hypofractionated and conventional fractionated radiation therapy in patients with implant-based breast reconstruction: A systematic review and meta-analysis

Seong-Hyuk Park [a,1], Yun-Jung Yang [b,1], Sihyun Sung [c], Yelim Choi [c], Eun-Jung Yang [a,*]

[a] Department of Plastic & Reconstructive Surgery, Institute of Innovative Digital Healthcare, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

[b] Department of Convergence Science, College of Medicine, Catholic Kwandong University International St. Mary's Hospital, Incheon, Republic of Korea

[c] Department of Research and Development, Seoul Medical Informatics Intelligence Lab Inc, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Postoperative complications
Radiation therapy
Breast reconstruction
Systematic review
Meta-analysis

ABSTRACT

Introduction: Post-mastectomy radiation therapy is an important component of adjuvant therapy for high-risk patients. However, radiation to reconstructed breasts can cause various complications. Recently, hypofractionated (HF) protocols have been adopted in several countries. Here, we aimed to assess the impact of HF protocols on implant-reconstructed breasts through a meta-analysis and systematic review of the currently available literature.

Methods: Records published until August 2023 were systematically searched in PubMed, Cochrane Library, and EMBASE databases. Keywords included hypofractionation radiotherapy, mastectomy, and breast reconstruction. Studies that utilized HF and conventional fractionation (CF) after prosthetic reconstruction were selected. Due to the rarity of events in outcomes, Mantel-Haenszel's odds ratios were calculated using a fixed-effect model to compare the complication rates between HF and CF groups. For analysis with high heterogeneity, a random effect model was used.

Results: Seven articles with 924 implant reconstructions, in which 506 (54.8 %) underwent HF were included. HF patients received 43.8 Gy on average, while CF patients received 51.2 Gy. Mean follow-up ranged from 10.6 to 35 months. Seven studies were included in the meta-analysis. HF groups had a significantly lower risk of capsular contracture (OR 0.25, 95 % CI 0.11–0.55), major revision surgery (OR 0.19, 95 % CI 0.05–0.80), and wound dehiscence (OR 0.24, 95 % CI 0.07–0.78) compared to CF groups. The risks of other complications were not statistically significant.

Conclusion: This study indicates that HF protocols are associated with fewer complications than CF protocols in implant-reconstructed patients. These findings suggest that the application of HF PMRT in implant-reconstructed patients with breast cancer is plausible.

List of abbreviations

PMRT	Post-mastectomy radiation therapy
HF	Hypofractionation
CF	Conventional fractionation
MINORS	Methodological index for non-randomized studies
ASTRO	American Society for Radiation Oncology
ESTRO	European Society for Radiotherapy and Oncology

1. Introduction

Breast cancer is the most prevalent cancer among females, with its incidence rising globally [1]. Improved survival rates have made adjuvant radiotherapy a critical component of multimodal treatment. Post-mastectomy radiation therapy (PMRT) is recommended for patients with locally advanced tumors, node-positive disease, or high recurrence risk, even after total mastectomy [2–5].

Reconstruction of the breast after mastectomy is not only an

* Corresponding author.
E-mail address: ENYANG7@yuhs.ac (E.-J. Yang).

[1] These authors contributed equally to this work

https://doi.org/10.1016/j.breast.2024.103782
Received 29 May 2024; Received in revised form 12 July 2024; Accepted 23 July 2024
Available online 23 July 2024

aesthetic procedure but is now regarded an essential part of breast cancer treatment, contributing to patient satisfaction and quality of life [6–8]. In the United States, implant-based immediate reconstruction is the most common procedure, and its popularity is increasing. However, PMRT is known to increase the risk of complications like infection, capsular contracture, and mastectomy flap necrosis. Most studies on PMRT and implant reconstruction have used conventional radiation protocols, delivering 40–50 Gy in 25 fractions [9]. This prolonged course of treatment results in greater inconvenience, decreased patient compliance, and increased healthcare costs [10–13].

Over the last two decades, clinical trials have extensively evaluated shortened courses of radiation therapy (RT) in the context of whole breast irradiation and chest wall RT [14–16]. HF protocols, typically delivering >2 Gy of radiation in 15–16 fractions, have gained global acceptance [17]. The American Society for Radiation Oncology (ASTRO) recommends hypofractionated radiotherapy for women aged >50 years with stage T1-2N0 not receiving chemotherapy. This eligibility was later expanded to include all women undergoing whole breast irradiation, regardless of chemotherapy history [18,19]. Also, the European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice consensus in 2022 has concluded upon consensus (86.9 %) and strong consensus (95.6 %) that HF can be offered for chest wall irradiation with or without reconstruction respectively [20]. Studies like the START A/B trials and reports from the US and China have confirmed its safety and efficacy compared with conventional radiation [14,15].

Despite widespread adoption, there is a lack of evidence regarding the safety of hypofractionated radiation for patients undergoing implant reconstruction [21]. This study aims to provide high-quality evidence to inform clinical practice and enhance understanding of optimal treatment strategies for these patients. Through a meta-analysis and systematic review, it comprehensively analyzes current literature on implant reconstruction-related complications associated with hypofractionated and conventional RT protocols.

2. Methods

2.1. Literature search protocols

Records were systematically identified through searches on PUBMED, Cochrane library, and EMBASE until August 2023. A combination of keywords were used for identification: (((Mastectomies OR Mastectomy OR Skin sparing Mastectomy OR Nipple-sparing Mastectomy) OR ("Mastectomy"[MeSH])) AND ((Breast reconstruction OR Breast reconstructions OR Reconstructed breast) OR ("Mammaplasty"[Mesh]))) AND ((Hypofractionation OR Hypofractionated OR Fractionation OR IMRT OR intensity modulated radiation therapy OR intensity-modulated radiation therapy OR VMAT OR volumetric modulated arc therapy OR volumetric-modulated arc therapy OR PMRT OR postmastectomy radiotherapy OR post-mastectomy radiotherapy) OR ("Dose Fractionation, Radiation"[MeSH] OR "Radiation Dose Hypofractionation"[MeSH] OR "Radiotherapy, Intensity-Modulated"[MeSH]))

2.2. Inclusion and exclusion criteria

Studies were included based on the following criteria: 1) Patients underwent prosthetic reconstruction after mastectomy, 2) The study population included patients receiving PMRT with hypofractionated protocols, and 3) Clinical data were readily available. Exclusion criteria were a) Reviews, case reports, comments, editorials, systematic reviews and meta-analyses, letters, surveys, and books, b) Ongoing clinical trials, c) Duplicate publications, and d) Studies not published in English.

2.3. Study selection

Title and abstract screening were conducted independently by two authors. Unrelated studies and those not meeting the criteria were excluded. Articles meeting the criteria underwent further assessment.

2.4. Data extraction

Selected articles were analyzed for relevant information, including the first author's name, publication year, country, general demographics, study design, radiation dosage, fractions, and follow-up duration. Study endpoints covered reconstruction-related complications such as seroma, hematoma, skin flap necrosis, implant loss, capsular contracture, breast pain, wound dehiscence, infection, cellulitis, and major revision surgery.

2.5. Quality assessment

The methodological index for non-randomized studies (MINORS) was used to assess the quality of the included studies [22]. The index included twelve items, which were scored as 0 (Not reported), 1 (reported but inadequate), and 2 (reported and adequate) for each item. Included were 1) clearly stated aim, 2) inclusion of consecutive patients, 3) prospective collection of data, 4) endpoints appropriate to the aim of the study, 5) unbiased assessment of the study endpoint, 6) follow-up period appropriate to the aim of the study, 7) loss to follow-up less than 5 %, 8) prospective calculation of the study size, 9) presence of adequate control group, 10) contemporary groups, 11) baseline equivalence of groups, and 12) adequate statistical analyses. All items were evaluated independently by two authors, and if any disagreement was present, it was settled by discussion between the two authors or consulting a third author. Quality of the study was determined as poor (≤14), moderated (15–22), or good (23≤).

2.6. Statistical analysis

Dichotomous outcomes, including cellulitis, capsular contracture, implant loss, infection, major revision surgery, and wound dehiscence, were compared between HF and CF groups and expressed as odds ratios (OR) with 95 % confidence intervals (CIs). Heterogeneity was evaluated using the I^2 test and Chi-square-based Q-test, with an I^2 value above 50 % and $p < 0.1$ indicating high heterogeneity. If heterogeneity was not found, Mantel-Haenszel**'s** (MH) ORs with 95 % CIs were calculated using a fixed effect model. Because MH OR is generally preferred when the effect size is small, particularly when the events are rare. A study in which zero complications of wound dehiscence, both HF and CF, were excluded from the meta-analysis as they are incompatible with MH OR [23]. For analysis with high heterogeneity, a random effect model was used. The fat necrosis, seroma, and skin flap necrosis rates could not be compared, as only one study reported each result [24,25]. Funnel plots and Egger's linear regression test assessed potential publication bias. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using STATA/MP v18 (StataCorp, College Station, TX, USA).

3. Results

3.1. Literature retrieval results

A total of 2010 articles were initially retrieved. After removing duplicates, 1525 articles remained. Of these, 1518 did not meet the inclusion criteria and were excluded from the analysis. Consequently, seven articles were included in the systematic review [24–30]. Of these, six reported complication rates and were included in the meta-analysis [24–26,28–30]. Fig. 1 provides a visual summary of the study process.

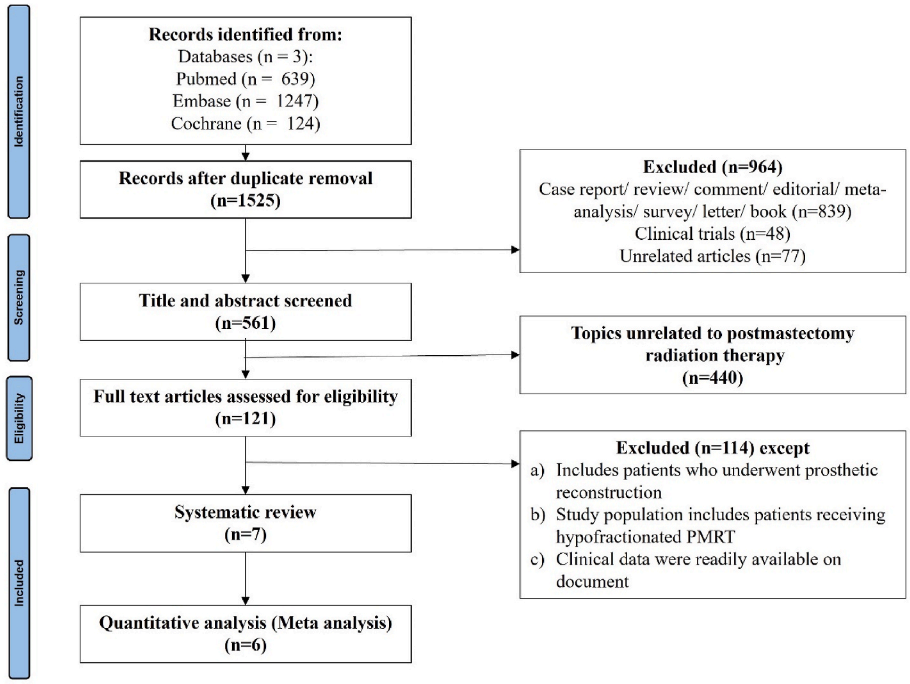

Fig. 1. Flow chart of literature search and selection.

3.2. Study characteristics

A total of seven articles, published between 2019 and 2023, were included (Table 1). Five studies were conducted in Korea and two in the US. All were retrospective studies. The analysis included 924 implant reconstructions, with 506 (54.8 %) undergoing HF. The mean patient age was 44.2 years. Patients receiving HF received an average of 43.8 Gy radiation, while those receiving conventional fractionation received an average of 51.2 Gy. The mean follow-up duration ranged from 10.6 to 35 months.

3.3. Methodological quality assessment

All included studies (n = 7) adequately described the aim of the research, including consecutive patients, endpoints according to the study aim, and the follow-up period (Table 2). The loss of follow-up rate was consistently below 5 % in all the studies. Chung et al. inadequately reported the assignment of the control group while adequately describing the baseline equivalence of the groups and statistical analyses [27]. All the included studies were judged to have a moderate risk of bias based on the MINORS scale.

3.4. Quantitative analysis

The HF group, compared to the CF group, showed significantly lower rates of capsular contracture (OR 0.25, 95 % CI 0.11–0.55, Fig. 2) [24–26,28,30] major revision surgery (OR 0.19, 95 % CI 0.05–0.80, Fig. 3) [26,28] and wound dehiscence (OR 0.24, 95 % CI 0.07–0.78, Fig. 4) [26,28]. Each was described in 5 studies (226 HF; 174 CF patients), 2 studies (105 HF; 54 CF patients), and 2 studies (105 HF; 54 CF patients), respectively. Wound dehiscence was reported in 2 studies but was excluded from analysis. Kim et al. did not differentiate between autologous and implant-based reconstruction, and Smith et al. reported no events available for analysis [24,25]. Cochran's Q-test was used to show inter-study heterogeneity. The results showed low heterogeneity for capsular contracture, major revision surgery, and wound dehiscence ($I^2 = 0.00$ %). Test of $\theta_i = \theta_j$ and test of $\theta = 0$ also showed no inter-study variance. The rates of cellulitis, implant loss, and infection did not differ significantly between the HF and CF groups (Table 3). Implant loss and infection showed heterogeneity between effect sizes and were analyzed using a random-effects model. The MH OR for the hematoma rate was not calculated because no events were reported in the HF arm.

3.5. Qualitative analysis

Data on skin flap necrosis, fat necrosis, lymphedema, and seroma formation were available in one article each. Smith et al. reported seroma requiring intervention, such as aspiration or re-surgery, in both HF and CF groups [24]; 14.3 % of patients treated with HF had seroma, compared with 5.4 % of CF patients. However, mastectomy skin flap necrosis occurred only in patients who underwent the CF protocol (5.4 %).

Although not included in the quantitative analysis, Chang et al. reported that overall complication rates were lower for HF (14.3 %) than CF (38.5 %, p = 0.017) [26]. The rates of breast-related complications and major complications were described by Kim et al. (2022), but they did not further specify the incidence of each outcome. The incidence of major breast complications did not differ significantly between the CF and HF groups [31].

4. Discussion

In this study, we conducted a systematic review and meta-analysis to investigate the impact of PMRT with HF protocols on patients undergoing implant-based reconstruction. Our findings show a significantly lower risk of capsular contracture, wound dehiscence, and a reduced incidence of major revision surgery in the HF group compared to the CF group.

Radiation is a crucial element in breast cancer treatment. The use of RT after mastectomy has increased with better local control and survival [2]. The conventional protocol delivers 1.8–2 Gy of radiation over 25 fractions, with or without a boost of 16 Gy. The linear-quadratic model estimates the effects of fractionation on cell survival, based on the 'α/β ratio.' Breast cancer cells, with a higher α/β ratio, are less spared by fractionation compared to normal cells. Twenty-five fractions typically take about 5 weeks to complete [12,17,32].

Table 1
General characteristics of included studies.

First author (year)	Country	Publication type	Study design	Age (years)	BMI (kg/m^2)	No. of implant based reconstruction		Radiation dose (Gy)		Fractionation		Dose per Fraction (Gy)		Follow-up duration (month)
						HF	CF	HF	CF	HF	CF	HF	CF	
Barnes et al., [2023] [30]	USA	Journal	Retrospective	45.2 (9.7)[a]	23.5 (4.5)[a]	6	64	42.56	50	16	25	2.67	2	17.9 (10.6)[a]
Chang et al., [2019] [26]	Korea	Journal	Retrospective	40 (10)[b]	21.6 (2.9)[b]	50	25	40.05 42.72	50.4	15 16	28	2.67	1.8	32.5 (17.2–72.5)[c]
Chung et al., [2021] [27]	Korea	Journal	Retrospective	44 (23–69)[c]	22.6 (15.7–35.6)[c]	105	209	40.05 42.56 45.9 48	45≤, <50 50 50<	15 16 17 20	25	2.4–2.7	1.8–2.0	- +
Kim et al., [2021] [25]	Korea	Journal	Retrospective	45.1 (22–74)[c]	- +	101	19	44.3 (40.5–48.6)[c]	50.3 (50–66)[c]	15 or 16	25	2.4–2.7	1.8–2.0	32.3 (4.8–118.5)[c]
Kim et al., [2022] [29]	Korea	Journal	Retrospective	- +	- +	175	35	46.6 (42.0–55.2)[c]	53.1 (50–66)[c]	15 or 16	25	2.4–2.7	1.8–2.0	35.3 (8.8–122.7)[c]
Smith et al., [2019] [24]	USA	Journal	Retrospective	49 (44–58)[b]	26 (22–30)[b]	14	37	45	50	15	25	3	2	19 (15–26)[b]
Song et al., [2020] [28]	Korea	Journal	Retrospective	41.3 (2.3)[a]	21.2 (0.73)[a]	55	29	40.05	50.4	15	28	2.67	1.8	34.8 (2.3)[a]

+data not described.
[a] Mean (Standard deviation).
[b] Median (Interquartile range).
[c] Median (Range).

While autologous reconstructions generally pose lower long-term complication risks [33], many patients choose implants due to shorter surgery duration, lower costs, and no donor site morbidity [34,35]. However, radiation increases the risk of complications like capsular contracture and infection [36]. Heterogeneity in radiation modality, fractionation, and boost can impact reconstruction outcomes [37]. In implant-reconstructed patients, the implant and acellular dermal matrix (ADM) could also be considered organs at risk, making the delineation of the target volume of great importance [38]. Recent studies suggest breast cancer cells may have a lower α/β ratio than expected, prompting proposals for fewer fractions with larger doses [17]. HF protocols, delivering 15–16 fractions, offer similar effects, lower costs, and higher patient compliance. A phase 3 trial found HF non-inferior with similar toxicities compared to CF in high-risk breast cancer patients [15,18,39,40].

Capsular contracture is common in prosthetic reconstruction, affecting 13.9 % of patients with subpectoral implants and 8.7 % with prepectoral implants using ADM [41]. PMRT is known to increase this proportion by up to 40 % [42]. Capsular contracture causes discomfort, firmness, severe distortion, and significant pain. Baker grades III and IV often require surgical intervention, such as capsulectomy with or without implant change.

Although not fully understood, chronic inflammation and subclinical infection are believed to be the main causes of capsular contracture [43,44]. The hydrophilic surfaces of silicone implants are prone to biofilm formation, triggering persistent immune reactions [45,46]. Residual seroma or hematoma from silicone shedding also causes excessive inflammation [44,47–49]. Furthermore, patients with hypertrophic scars are at higher risk of capsular contracture [50]. Studies have shown that Radiation-induced tissue injury increases gene expression related to scar formation and fibrosis, including TGF-β1 and MECP2, leading to a higher risk of capsular contractures [51,52]. Additionally, a previous report showed less radiodermatitis and radiation-induced fibrosis in patients receiving radiation with reduced fractionated schedules, possibly due to decreased total dosage to surrounding tissue, which may explain the lower capsular contracture rates with hypofractionated protocols in our study [53].

Despite these findings, Smith et al., reported a higher incidence of capsular contracture in patients who received the HF protocol [24]. This discrepancy may be attributed to the small number of patients in each subgroup. Interestingly, no cases of capsular contracture were reported in 37 patients and 42 non-radiated patients, with one case among 14 HF patients, which is lower than the general incidence.

Recent study suggests that prepectoral implant placement significantly lowers the risk of capsular contracture after PMRT [54]. However, the study does not distinguish implant placement according to radiation method, making it hard to elaborate its effects. Additionally, radiation delivered via protons may have different consequences compared to photon radiation [55]. Kim et al. reported an exceptionally low incidence of capsular contracture, counting only cases requiring re-operation or admission, which may explain the low rate, as not all grade III contractures undergo such treatment [25].

The rate of wound dehiscence and incidence of major revision surgeries, including implant change, removal, and switch to autologous reconstruction, were also lower in patients who received HF, according to our study results. Major revision surgeries in prosthetic reconstruction are mainly influenced by the viability of the mastectomy flap over the implant. Similar to capsular contracture, the HF protocol could result in less radiation exposure to surrounding tissue due to a lower net radiation dose compared to the CF protocol [56]. While it is difficult to explain the exact etiology, this may also be related to a reduced biological equivalent dosage to normal tissues. However, revision surgery is also a risk factor that can cause reconstruction failure. Thus, HF can be advantageous for implant reconstruction from a plastic surgery point of view.

The odds ratios for cellulitis, implant loss, and infection rates were not significant in the analysis. The limited number of included studies

Table 2
Risk of bias assessment for included studies based on methodological index for non-randomized studies score.

Items		Barnes, L. L. et al. [2023] [30]	Chang, J. S. et al. [2019] [26]	Chung, S. Y. et al. [2021] [27]	Kim, D. Y. et al. [2021] [25]	Kim, D. Y. et al. [2022] [31]	Smith, N. L. et al. [2019] [24]	Song, S. Y. et al. [2020] [28]
1	A clearly stated aim	2	2	2	2	2	2	2
2	Inclusion of consecutive patients	2	2	2	2	2	2	2
3	Prospective collection of data	0	0	0	0	0	0	0
4	Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2
5	Unbiased assessment of the study endpoint	0	2	0	2	2	0	0
6	Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2
7	Loss to follow up less than 5 %	2	2	2	2	2	2	2
8	Prospective calculation of the study size	0	0	0	0	0	0	0
9	An adequate control group	2	2	1	2	2	2	2
10	Contemporary groups	2	2	2	2	2	2	2
11	Baseline equivalence of groups	1	1	1	2	2	1	1
12	Adequate statistical analyses	1	1	1	2	2	1	1
Total score		20	18	15	20	20	16	16
Maximum score		24	24	24	24	24	24	24

*0: Not reported; 1: reported but inadequate; 2: reported and adequate; Quality of the study was determined as poor (≤14), moderated (15–22), or good (23≤).

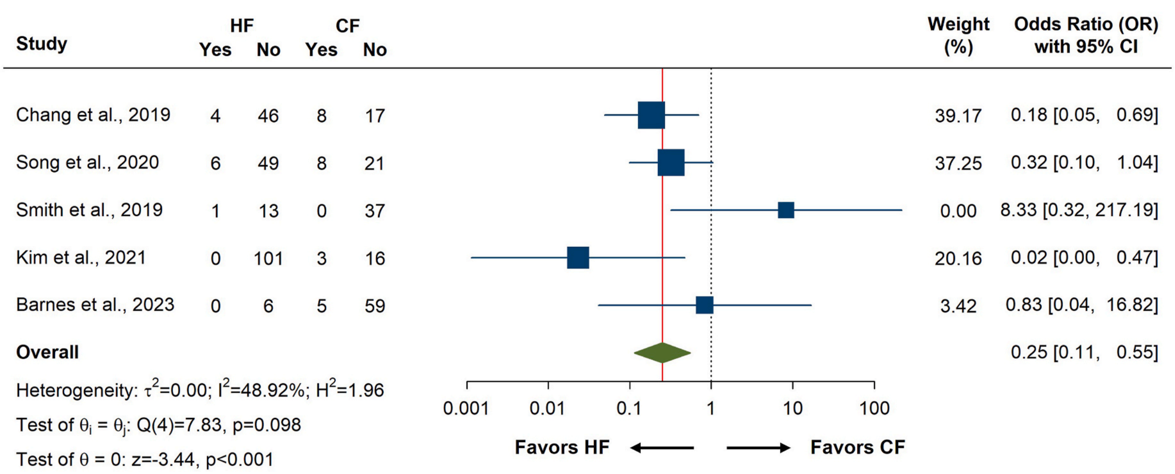

Fig. 2. Forest plot comparing incidence of capsular contracture between HF and CF groups.

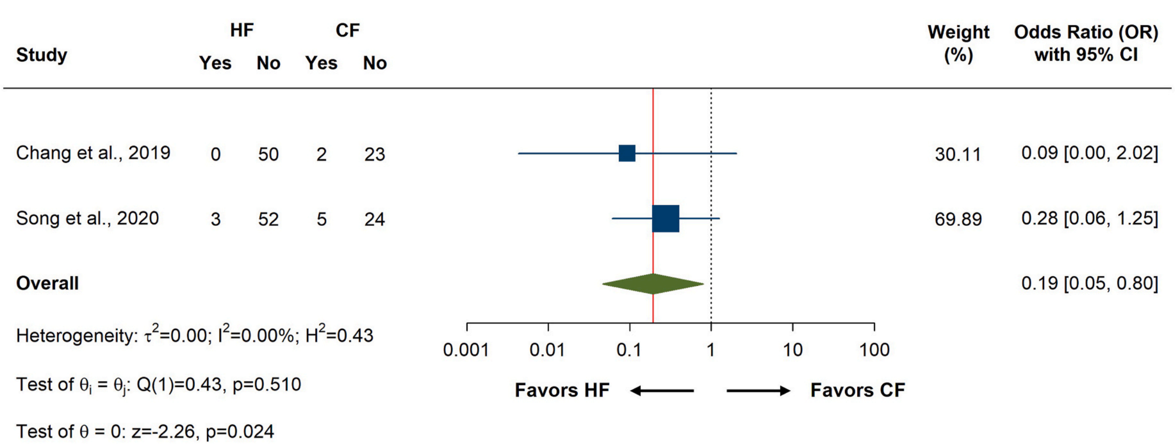

Fig. 3. Forest plot comparing incidence of major revisional surgery between HF and CF groups.

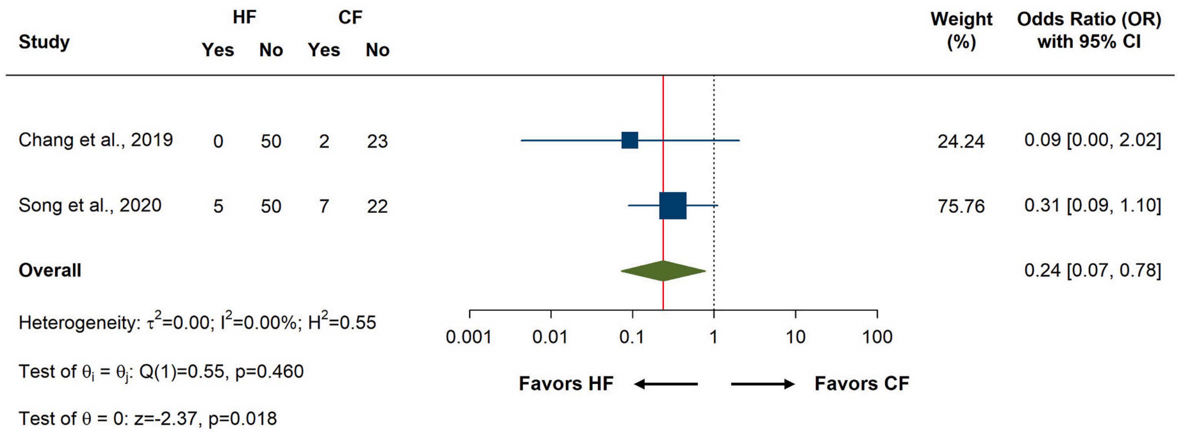

Fig. 4. Forest plot comparing the incidence of wound dehiscence between HF and CF groups.

Table 3
Summary of the results from meta-analysis on postoperative complications between hypofractionated radiation and conventional radiation.

Outcome measures	Studies	HF (n)		CF (n)		OR	Heterogeneity				Ref
	(n)	Events (%)	Total	Events (%)	Total	(95 % CI)	Q	df	$P_{\text{-hetero}}$	I^2 (%)	
Cellulitis	2	5 (4.8)	105	2 (3.7)	54	1.29 (0.24, 6.91)	0.05	1	0.83	0.00	Chang [2019] [26] Song [2020] [28]
Implant loss[a]	3	8 (6.6)	121	15 (12.5)	120	1.13 (0.14, 9.43)	7.52	2	0.02	71.81	Smith [2019] [24] Kim [2021] [25] Barnes [2023] [30]
Infection[a]	4	12 (9.6)	125	28 (18.1)	155	0.95 (0.19, 4.75)	8.78	3	0.03	65.70	Smith [2019] [24] Chang [2019] [26] Song [2020] [28] Barnes [2023] [30]

HF=Hypofractionated radiation, CF=Conventional radiation, OR = odds ratio, CI = confidence interval, Q = homogeneity test, df = degree of freedom, $P_{\text{-hetero}}$ = probability level associated with the Q test.
[a] Random effect model was applied.

makes it challenging to determine the exact cause of the variance. One possible explanation is that Smith et al. reported an exceptionally high rate of infection in hypofractionated patients (8/14 = 57.1 %). However, the authors did not identify the reason for the increased rate compared to conventional patients (8/37 = 21.6 %).

In their qualitative analysis, Smith et al. reported a higher rate of seroma in the HF group, but their interpretation is limited owing to the small sample size. Chang et al. demonstrated that the survival rate of patients receiving PMRT after reconstruction was not significantly different except, for the 3-year disease-free survival, which was higher for the HF group than the CF group, aligning with previous studies like the START-A/B trials [16].

Although not included in the analysis, Anderson et al. reported that fractionation protocols were not related to the risk of implant failure in patients who underwent implant-based reconstruction and received PMRT [57]. In 2009, Whitfield reported a significantly higher rate of severe capsular contracture after hypofractionated PMRT (19.5 % in radiated patients compared to 0 % in non-irradiated patients). This may have contributed to the hesitation to use HF protocols in implant reconstruction. However, they only included subpectoral or latissimus dorsi flaps with implant reconstruction before the introduction of acellular dermal matrices [58]. Rojas et al. reported an incidence of grade IV capsular contractures of 8.6 % in radiated breasts versus 3.9 % in non-irradiated patients. The reconstruction failure rate was significantly higher in patients who had an expander inserted compared to those who did not (12.9 % vs. 1.6 %). Overall, the authors concluded that HF was not detrimental to reconstruction outcomes [59]. In terms of local control, Poppe et al. reported a 92 % local recurrence-free survival and 90 % 5-year overall survival in HF patients without significant radiation toxicities [60,61].

This study had several limitations. Firstly, we included a limited number of articles comparing HF and CF protocols in patients undergoing implant reconstruction, and all included studies were retrospective. This is likely because the HF protocol only began to be applied in the 2000s, making its implementation period shorter than that of the CF protocol, and concerns about its effects on reconstructed implants have only recently emerged [26]. Nevertheless, we included most relevant articles and analyzed the results both quantitatively and qualitatively.

Secondly, our study did not differentiate between the planes of reconstruction or whether it was one- or two-stage reconstruction for prosthetic reconstructions. There is conflicting evidence regarding which protocol is preferred in the setting of PMRT. Given the known differences in complication rates, a detailed analysis with a larger sample size is necessary [33].

Furthermore, not all potential adverse effects could be discussed in this study. Differences in fraction dose may affect radiodermatitis rates, cosmetic outcomes, and lymphedema. Although there was no description in reconstructed patients, several studies showed lower rates of grade 2 radiodermatitis and fibrosis in HF compared to CF [40,62]. Additionally, Byun et al. reported an increased rate of lymphedema when treated with CF [63].

To address these limitations, several prospective clinical trials are currently underway. These include the RT-CHARM (NCT03414970) phase III randomized trial, Hypo Versus Conventional Fractionation in Reconstructed-Breast Cancer Mastectomy Patients (NCT05253170). These studies are expected to provide more insights into the application and effects of HF protocols [24].

Scoping the current knowledge can help guide further implementation of HF protocols. Even with the small number of included studies, there is a clear trend that HF is non-inferior to CF regarding reconstruction-related complications and may be safer concerning major revision surgery rates and the incidence of capsular contractures. Randomized controlled trials comparing HF and CF in patients who underwent implant reconstruction are currently underway. Further large-scale studies could clarify the definitive effects of HF.

5. Conclusion

In conclusion, PMRT with the HF protocol resulted in significantly less capsular contractures, wound dehiscence, and major revision surgery than with conventional protocols. These findings suggest that the application of HF PMRT in implant-reconstructed patients with breast cancer is plausible. Further prospective studies are warranted to confirm this hypothesis.

Funding

This work was supported by the Technology and Development Program (RS-2023-00222788) funded by the Ministry of SMEs and Startups (MSS, Korea).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Seong-Hyuk Park: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Yun-Jung Yang:** Methodology, Formal analysis, Data curation, Conceptualization. **Sihyun Sung:** Formal analysis, Data curation. **Yelim Choi:** Formal analysis, Data curation. **Eun-Jung Yang:** Writing – review & editing, Writing – original draft, Supervision, Methodology.

Acknowledgements

We would like to thank Da-mi Jeong, PhD (Librarian, Yonsei University Medical Library, Seoul, Korea) for her generous help in the searching process.

References

[1] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
[2] McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
[3] Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–8.
[4] Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949–55.
[5] Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956–62.
[6] Susarla SM, Ganske I, Helliwell L, Morris D, Eriksson E, Chun YS. Comparison of clinical outcomes and patient satisfaction in immediate single-stage versus two-stage implant-based breast reconstruction. Plast Reconstr Surg 2015;135:1e–8e.
[7] Jagsi R, Jiang J, Momoh AO, Alderman A, Giordano SH, Buchholz TA, et al. Complications after mastectomy and immediate breast reconstruction for breast cancer: a claims-based analysis. Ann Surg 2016;263:219–27.
[8] Jagsi R, Jiang J, Momoh AO, Alderman A, Giordano SH, Buchholz TA, et al. Trends and variation in use of breast reconstruction in patients with breast cancer undergoing mastectomy in the United States. J Clin Oncol 2014;32:919–26.
[9] Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:691–722.
[10] Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol 1985;58:515–28.
[11] Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679–94.
[12] Bentzen SM, Joiner MC. The linear-quadratic approach in clinical practice. Basic clinical radiobiology: CRC Press 2018:112–24.
[13] Matthews JH, Meeker BE, Chapman JD. Response of human tumor cell lines in vitro to fractionated irradiation. Int J Radiat Oncol Biol Phys 1989;16:133–8.
[14] Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331–41.
[15] Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371:1098–107.
[16] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94.
[17] Moran MS, Truong PT. Hypofractionated radiation treatment for breast cancer: the time is now. Breast J 2020;26:47–54.
[18] Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018;8:145–52.
[19] Massabeau C, Fournier-Bidoz N, Wakil G, Castro Pena P, Viard R, Zefkili S, et al. Implant breast reconstruction followed by radiotherapy: can helical tomotherapy become a standard irradiation treatment? Med Dosim 2012;37:425–31.
[20] Meattini I, Becherini C, Boersma L, Kaidar-Person O, Marta GN, Montero A, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol 2022;23:e21–31.
[21] Kronowitz SJ. Current status of implant-based breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2012;130. 513e-23e.
[22] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712–6.
[23] Higgins J, Thomsas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions Cochrane. 2023.
[24] Smith NL, Jethwa KR, Viehman JK, Harmsen WS, Gonuguntla K, Elswick SM, et al. Post-mastectomy intensity modulated proton therapy after immediate breast reconstruction: initial report of reconstruction outcomes and predictors of complications. Radiother Oncol 2019;140:76–83.
[25] Kim DY, Park E, Heo CY, Jin US, Kim EK, Han W, et al. Hypofractionated versus conventional fractionated radiotherapy for breast cancer in patients with reconstructed breast: toxicity analysis. Breast 2021;55:37–44.
[26] Chang JS, Song SY, Oh JH, Lew DH, Roh TS, Kim SY, et al. Influence of radiation dose to reconstructed breast following mastectomy on complication in breast cancer patients undergoing two-stage prosthetic breast reconstruction. Front Oncol 2019;9.
[27] Chung SY, Chang JS, Shin KH, Kim JH, Park W, Kim H, et al. Impact of radiation dose on complications among women with breast cancer who underwent breast reconstruction and post-mastectomy radiotherapy: a multi-institutional validation study. Breast 2021;56:7–13.
[28] Song SY, Chang JS, Fan KL, Kim MJ, Chang HP, Lew DH, et al. Hypofractionated radiotherapy with volumetric modulated arc therapy decreases postoperative complications in prosthetic breast reconstructions: a clinicopathologic study. Front Oncol 2020;10.
[29] Kim DY, Park E, Heo CY, Jin US, Kim EK, Han W, et al. Influence of hypofractionated versus conventional fractionated postmastectomy radiation therapy in breast cancer patients with reconstruction. Int J Radiat Oncol Biol Phys 2022;112:445–56.
[30] Barnes LL, Chew J, Lem M, Park C, Yang JC, Prionas N, et al. Modifiable post-mastectomy radiation therapy factors and impact on implant-based breast reconstruction outcomes. Plast Reconstr Surg 2023. https://doi.org/10.1097/PRS.0000000000010824.
[31] Kim N, Kim H, Park W, Choi DH, Cho WK, Nam SJ, et al. Immediate breast reconstruction has no impact on the oncologic outcomes of patients treated with post-mastectomy radiation therapy: a comparative analysis based on propensity score matching. Breast Cancer Res Treat 2022;192:101–12.

[32] McMahon SJ, Prise KM. Mechanistic modelling of radiation responses. Cancers 2019;11:205.

[33] Weber WP, Shaw J, Pusic A, Wyld L, Morrow M, King T, et al. Oncoplastic breast consortium recommendations for mastectomy and whole breast reconstruction in the setting of post-mastectomy radiation therapy. Breast 2022;63:123–39.

[34] Hershenhouse KS, Bick K, Shauly O, Kondra K, Ye J, Gould DJ, et al. Systematic review and meta-analysis of immediate versus delayed autologous breast reconstruction in the setting of post-mastectomy adjuvant radiation therapy. J Plast Reconstr Aesthetic Surg 2021;74:931–44.

[35] Palve JS, Luukkaala TH, Kääriäinen MT. Autologous reconstructions are associated with greater overall medium-term care costs than implant-based reconstructions in the Finnish healthcare system: a retrospective interim case-control cohort study. J Plast Reconstr Aesthetic Surg 2022;75:85–93.

[36] Nelson JA, Disa JJ. Breast reconstruction and radiation therapy: an update. Plast Reconstr Surg 2017;140. 60s-8s.

[37] Ho AY, Hu ZI, Mehrara BJ, Wilkins EG. Radiotherapy in the setting of breast reconstruction: types, techniques, and timing. Lancet Oncol 2017;18:e742–53.

[38] Kaidar-Person O, Offersen BV, Hol S, Arenas M, Aristei C, Bourgier C, et al. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother Oncol 2019;137:159–66.

[39] Zhang L, Jin K, Wang X, Yang Z, Wang J, Ma J, et al. The impact of radiotherapy on reoperation rates in patients undergoing mastectomy and breast reconstruction. Ann Surg Oncol 2019;26:961–8.

[40] Wang SL, Fang H, Song YW, Wang WH, Hu C, Liu YP, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019;20:352–60.

[41] Ribuffo D, Berna G, De Vita R, Di Benedetto G, Cigna E, Greco M, et al. Dual-plane retro-pectoral versus pre-pectoral DTI breast reconstruction: an Italian multicenter experience. Aesthetic Plast Surg 2021;45:51–60.

[42] Sinnott CJ, Persing SM, Pronovost M, Hodyl C, McConnell D, Ott Young A. Impact of postmastectomy radiation therapy in prepectoral versus subpectoral implant-based breast reconstruction. Ann Surg Oncol 2018;25:2899–908.

[43] Virden CP, Dobke MK, Stein P, Parsons LC, Frank DH. Subclinical infection of the silicone breast implant surface as a possible cause of capsular contracture. Aesthetic Plast Surg 2020;44:1141–7.

[44] Moyer HR, Ghazi BH, Losken A. The effect of silicone gel bleed on capsular contracture: a generational study. Plast Reconstr Surg 2012;130:793–800.

[45] Costerton JW, Stewart PS. Battling biofilms. Sci Am 2001;285:74–81.

[46] Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis 2002;8:881–90.

[47] Headon H, Kasem A, Mokbel K. Capsular contracture after breast augmentation: an update for clinical practice. Arch Plast Surg 2015;42:532–43.

[48] Dower R, Turner ML. Pilot study of timing of biofilm formation on closed suction wound drains. Plast Reconstr Surg 2012;130:1141–6.

[49] Daar DA, Bekisz JM, Chiodo MV, DeMitchell-Rodriguez EM, Saadeh PB. Hematoma after non-oncologic breast procedures: a comprehensive review of the evidence. Aesthetic Plast Surg 2021;45:2602–17.

[50] Zikiryakhodzhaev AD, Alekseeva GS, Reshetov IV, Starkova MV, Saribekyan EK, Usov FN, et al. Botulinum toxin type A as a tool for correcting capsular contracture after reconstructive breast surgery. Plast Reconstr Surg Glob Open 2021;9:e3372.

[51] Weigel C, Schmezer P, Plass C, Popanda O. Epigenetics in radiation-induced fibrosis. Oncogene 2015;34:2145–55.

[52] Safran T, Nepon H, Chu CK, Winocour S, Murphy AM, Davison PG, et al. Current concepts in capsular contracture: pathophysiology, prevention, and management. Semin Plast Surg 2021;35:189–97.

[53] Allali S, Kirova Y. Radiodermatitis and fibrosis in the context of breast radiation therapy: a critical review. Cancers 2021;13.

[54] Sobti N, Weitzman RE, Nealon KP, Jimenez RB, Gfrerer L, Mattos D, et al. Evaluation of capsular contracture following immediate prepectoral versus subpectoral direct-to-implant breast reconstruction. Sci Rep 2020;10:1137.

[55] Naoum GE, Ioakeim MI, Shui AM, Salama L, Colwell A, Ho AY, et al. Radiation modality (Proton/Photon), timing, and complication rates in patients with breast cancer receiving 2-stages expander/implant reconstruction. Practical Radiation Oncology 2022;12:475–86.

[56] Nahum AE. The radiobiology of hypofractionation. Clin Oncol 2015;27:260–9.

[57] Anderson JD, Hammond JB, Kosiorek HE, Thorpe CS, Bhangoo RS, Pockaj BA, et al. Unplanned implant removal in locally advanced breast cancer. Breast J 2021;27:466–71.

[58] Whitfield GA, Horan G, Irwin MS, Malata CM, Wishart GC, Wilson CB. Incidence of severe capsular contracture following implant-based immediate breast reconstruction with or without postoperative chest wall radiotherapy using 40 Gray in 15 fractions. Radiother Oncol 2009;90:141–7.

[59] Rojas DP, Leonardi MC, Frassoni S, Morra A, Gerardi MA, La Rocca E, et al. Implant risk failure in patients undergoing postmastectomy 3-week hypofractionated radiotherapy after immediate reconstruction: implant failure after breast hypofractionated radiotherapy. Radiother Oncol 2021;163:105–13.

[60] Khan AJ, Poppe MM, Goyal S, Kokeny KE, Kearney T, Kirstein L, et al. Hypofractionated postmastectomy radiation therapy is safe and effective: first Results from a prospective phase II trial. J Clin Oncol 2017;35:2037–43.

[61] Poppe MM, Yehia ZA, Baker C, Goyal S, Toppmeyer D, Kirstein L, et al. 5-Year update of a multi-institution, prospective phase 2 hypofractionated postmastectomy radiation therapy trial. Int J Radiat Oncol Biol Phys 2020;107:694–700.

[62] Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: the DBCG HYPO trial. J Clin Oncol 2020;38:3615–25.

[63] Byun HK, Chang JS, Im SH, Kirova YM, Arsene-Henry A, Choi SH, et al. Risk of lymphedema following contemporary treatment for breast cancer: an analysis of 7617 consecutive patients from a multidisciplinary perspective. Ann Surg 2021;274:170–8.