



Implant-based immediate breast reconstruction: failure rate when radiating the tissue expander or the permanent implant—a meta-analysis

Víctor Fuertes¹, Mónica Francés², José M. Casarrubios², Javier Fernández-Palacios², Jesús María González³, Juan Francisco Loro-Ferrer⁴

¹Department of Plastic Surgery, Vancouver General Hospital, Vancouver, Canada; ²Department of Plastic Surgery, ³Research Department, University Hospital Dr. Negrín, Las Palmas de Gran Canaria, Spain; ⁴Clinical Pharmacology, Medicine School-University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

Contributions: (I) Conception and design: V Fuertes; (II) Administrative support: J Fernández-Palacios, JF Loro-Ferrer; (III) Provision of study materials or patients: V Fuertes; (IV) Collection and assembly of data: V Fuertes, M Francés, JM Casarrubios; (V) Data analysis and interpretation: V Fuertes, JM González; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Víctor Fuertes. Plastic, Reconstructive & Aesthetic Surgery Specialist Physician. Department of Plastic Surgery (International Fellow), Vancouver General Hospital, Vancouver, Canada. Email: vfuertesbielsa@gmail.com.

Background: Implant-based immediate approach remains to be a first line option for reconstruction of mastectomy defects. When combined with post-mastectomy radiation therapy (PMRT) two different schemas are possible: radiating the temporary tissue expander (TTE) or the permanent implant (PI). The present article intends to be the biggest cohort meta-analysis to the date comparing reconstructive failure (RF) rate in these two scenarios: PMRT to TE compared with PMRT to PI.

Methods: A systematic search of the literature was performed on PUBMED/MEDLINE. The following key words were chosen: Breast Reconstruction AND Implant based AND Immediate. The time limit applied was from January 2008 to January 2019. We selected ten articles (n=1,130) to perform a meta-analysis due to the similarity of their approaches. Secondly, we did a simple literature review in order to identify some variables possibly working as predicting factors for RF.

Results: Previous meta-analysis are analysed. Some variables possibly working as risk factors for RF are summarized. We performed a meta-analysis in two scenarios: a fixed-effect model and a random effect model. For the random effect model an OR of 1.85 was obtained (0.96, 3.57; P=0.067). A funnel plot is performed showing no publication bias exists.

Conclusions: There is a tendency towards a higher RF rate when the TTE is irradiated compared with the irradiation of the PI. Further studies trying to elucidate the influence of the suggested risk factors for RF have to be performed to establish a consensus about the indications and contraindications of this reconstructive modality.

Keywords: Breast reconstruction; failure; implant; meta-analysis; radiotherapy

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Introduction

Mastectomies due to breast cancer and as contralateral prophylactic procedures have grown up during the last few years in the United States (1,2). Parallel to this, several randomized trials in the field of Radiation Oncology have diminished the threshold for recommending post-mastectomy radiation therapy (PMRT) from four-or-more positive axillary lymph node to the current recommendation (one-to-three), due to its probed capacity to decrease local recurrence and to improve survival rate (3-7).

Two steps prosthesis-based immediate or delayed breast reconstruction remains a regular procedure. During the decade 1998–2008, it was the most common reconstructive option in the States, even ahead of autologous reconstructions (8,9). Different papers had demonstrated its oncological safety (10), good satisfaction levels from the cosmetic point of view as well as acceptable long-term outcomes (11). Thus, this reconstructive modality should be considered as a first line option for mastectomy reconstruction.

Even in the setting of the irradiated patient population, Agarwal *et al.* (12) demonstrated an increase in prosthesis-based reconstruction from 27% to 52%, with the subsequent decrease in autologous reconstruction, over the past 10 years.

Immediate breast reconstruction improves patient body self-image and overall psychological well-being when compared with the delayed modality. Moreover, this reconstructive technique doesn't compromise the delivery of PMRT (13).

Concerns regarding the outcome of patients with a history of irradiation prior to the reconstruction or PMRT have motivated an important amount of papers during the last years, mainly in the context of Implant-based Immediate Breast Reconstruction (9,14-17). Its pathological effects during an acute and a chronic phase have been well described (18), with a maximal loss of endothelial cell and subsequent dermal deleterious changes occurring from months 2 to 6 (19). The combination of PMRT and Implant-based Immediate Breast Reconstruction has demonstrated to produce an increase in reconstructive failure (RF) rate as well as in some other complications (capsular contracture, infection...) (20-22). RF is mainly defined as the removal of implants with the inability to replace them, resulting in no final reconstruction or the need to add new salvage procedures. Nevertheless, its oncological safety and overall good patients and surgeon's

satisfaction rates suggest not considering the need for PMRT as a primary universal contraindication for Implant-based Immediate Breast Reconstruction (23).

In the last few years, there has been an increase in the group of patients undergoing a mastectomy and an expander implantation in whom the need of PMRT remains uncertain (Mostly, Stage II Breast Cancer treated with neoadjuvant chemotherapy and undetermined lymph nodes status at the time of the surgery) (3). In addition, not all patients desire to delay breast reconstruction when radiotherapy is needed, nor some of them are willing/are candidates to undergo complex flap-based reconstructions.

Two different approaches regarding the timing of PMRT in the Implant-based Immediate Breast Reconstruction have been applied. The first consists of irradiation of the temporary tissue expander (TTE), and applying the radiotherapy during the expansion stage (RT to TTE), prior to TTE exchange to permanent implant (PI). This is the most common approach. The second approach consists of irradiating the PI when expansion stage and TTE-PI exchange procedure have already been completed (RT to PI). The latter is mainly used if adjuvant chemotherapy is being administered to the patient because it allows more time for the expansion (during the chemotherapy sessions) and makes safer the delay of the PMRT from 8 weeks up to 6 months after the end of the adjuvant chemotherapy (13,24). The success of this sequence is very dependent in the coordination of the oncological team, which is not always easy to achieve. Its use is restricted in women receiving neoadjuvant chemotherapy as not more than 6 weeks from mastectomy to radiotherapy delivery could be accepted in this group in which a lot of them are suffering a stage III or more advanced breast cancer (3).

Several articles have compared cohorts using these two algorithms, focusing about which of them is better regarding the failure rate (25-34). From these papers, some meta-analysis has been performed but lack of consistent conclusions has been found due to several reasons (35-38). In addition, no further steps to analyze the predictors for the failure rate are available. Thus, this article, intends to be the largest cohort meta-analysis to date about the failure rate, contributing to new conclusions. *Is there a better time to irradiate when doing an immediate implant-based breast reconstruction? Should we ideally irradiate the TE or the PI?* By reviewing similar articles we also tried to elucidate question, *what are the main factors that could be related with RF in the setting of PMRT to PI/TTE?*

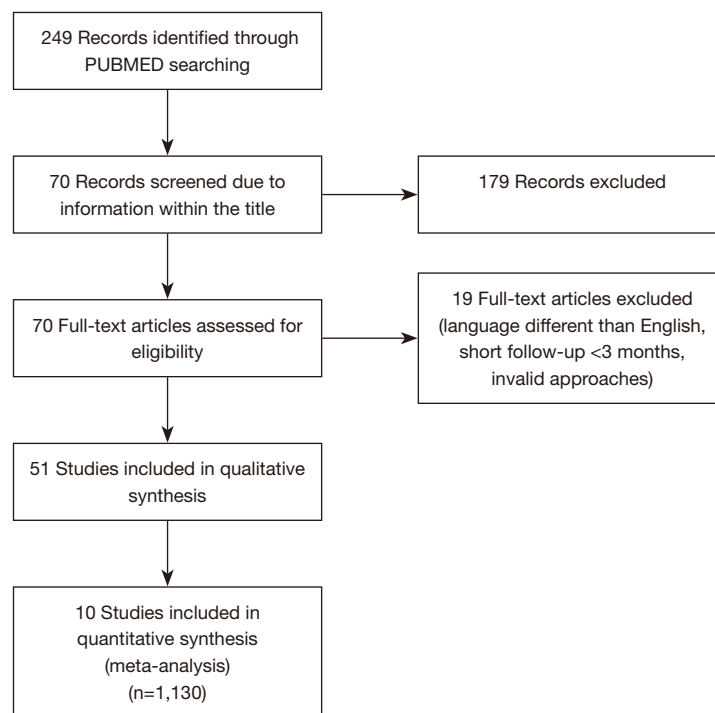


Figure 1 Flow chart.

Methods

A systematic search of the literature was performed on PUBMED/MEDLINE. The following key words were chosen: Breast Reconstruction AND Implant based AND Immediate. The time limit applied was from January 2008 to January 2019. A total of 249 results were found. We selected 51 of them. Articles not written in English, those not including at least one of RT schemas as well as those with short average follow-up times (less than 3 months) were excluded (*Figure 1*).

In the first part of the article, we selected ten articles (n=1,130) to perform a meta-analysis due to the similarity of their approaches. They are all Cohorts/Case-Controls retrospective or prospective studies comparing the failure rate when performing either the PMRT to TTE approach or the PMRT to the PI one. In order to ensure a better overall understanding we have calculated the odds ratio (OR) in every single study (PMRT to TTE versus PMRT to PI) as well as the weighted average of the ORs with 95% confidence intervals. The results are presented in a forest plot considering both a fixed and a random effect models. A sensitivity test by eliminating studies one by one is also performed. Finally, funnel plot and asymmetry tests are

done.

Secondly, we did a simple literature review in order to identify some variables possibly working as predicting factors for RF in the two different schemas. The differences in study designs made statistically complex to perform a multivariate meta-analysis.

The statistical software used was meta (39). A DerSimonian-Laird method was used for the meta-analysis and OR as measure of association. Statistical heterogeneity was analysed using the Mantel-Haenszel method/ I^2 statistic. Statistical significance was defined as $P < 0.05$. High heterogeneity is defined as $I^2 > 50\%$.

The present study design followed PRISMA guidelines.

Results

Literature review

Some previous attempts to perform a meta-analysis about failure rate depending on the RT timing were found.

Lam *et al.* (35) published a paper in which three articles directly comparing failure rate in the RT to PI group versus RT to TTE were included. They obtained an OR of 0.13 (0.05–0.32) showing that failure was significantly lower

(22.9% versus 5.6%, $P = \text{less than } 0.0001$) when irradiating the PI. The sample population was 131 patients. One of the studies included was a prospective nonrandomized trial which found three risk factors for RF: T3-T4 tumours, smoking and positive axillary lymph node status (40). An important rate of patients undergoing the schema RT to TTE had received neoadjuvant chemotherapy due to their stage III or more advanced cancer. Both variables (neoadjuvant chemotherapy/Stage III-IV) might act as confounder factors for RF and RT to TTE. A clear limitation regarding the sample size is present in this study.

El-Sabawi *et al.* (36) presented a paper trying to evaluate outcomes following autologous and implant-based reconstruction in the setting of PMRT and adjuvant chemotherapy. A pooled analysis using study size means was used. A total population of 3,605 patients was included for the implant-based reconstruction group. No difference about immediate or delayed reconstruction was made in this group. The analysis demonstrated a failure rate of 18.8% when PMRT preceded the TTE to PI exchange (RT to TTE), compared to a rate of 14.7% if the radiation was delivered to the PI ($P = 0.006$). In their paper they also analysed the impact of adjuvant chemotherapy on surgical outcomes. Results are unclear and further prospective and larger studies are required to elucidate if women requiring adjuvant chemotherapy have an increased risk of failure. This study included a larger number of studies leading to a better sample size. Otherwise, most of them are single arm studies with low levels of evidence and no direct comparison between the two groups. The resulting pooled analysis may conduct to wrong conclusions due to a different value of the weighting process.

Lee *et al.* (37) conducted a meta-analysis including 899 patients from double-arm previous studies directly comparing both schemas. Although they showed a tendency towards an increased risk of failure in the RT to TTE group (RR 1.72), their results were not statistically significant. They advocated larger population meta-analysis.

Ricci *et al.* (38) set in their study a double level analysis. In the first part, they conducted a pooled analysis from single arm studies data. They founded a failure rate of 20% versus 13.4%, $P = 0.001$ when comparing RT to TTE versus RT to PI. In the second part they did a meta-analysis with those studies that compared both groups, including a total population of 798 patients. They concluded a higher incidence of failure when the TTE was radiated: RR 2.33 (1.24–4.35), $P = 0.083$ for the random effect model; RR 2.31 (1.56–3.41), $P < 0.0001$ for the fixed effect model.

Ten articles were selected for our meta-analysis. All the studies included compare both groups, and no pooled analysis is done.

Anderson *et al.* (25) presented a failure rate of 4.8% when irradiating TTE, compared with a 0% failure rate when the radiation was applied to the PI ($P = 0.21$). No factors were significant predictors of failure. They hypothesized that their low failure rate could have been related with the use of intensity-modulated RT.

Nava *et al.* (26) demonstrated a statistically significant ($P < 0.0001$) increase in RF when irradiating TTE compared with RT to PI (40% vs. 6.4%).

Collier *et al.* (27) didn't found any differences when comparing failure risk in both groups (6.3% TTE vs. 4.5% PI; $P = 1$).

In their Cohorts study, Lentz *et al.* (28) showed up no differences when comparing failure (13.6% RT to PI vs. 20.6% RT to TTE, $P = 0.72$). Current smoking was the only predictor they found to be associated with an overall increased risk of complication. In the second part of their article they attempted to demonstrate differences in RF when the TTE to PI exchange was done in the first 4 months after the PMRT or after more than 4 months (for the RT to TTE group). Even when they found a tendency to an increased RF when doing the exchange in less than four months after the PMRT (25% vs. 14.9%), the results were not statistically significant. Similarly, Peled *et al.* (41,42) demonstrated a statistically significant increase in failure of 22.4% versus 7.7%, $P = 0.036$, in the group undergoing the exchange earlier after the PMRT (first 6 months). Kronowitz *et al.* (43) also stated a higher failure rate when the TE was replaced earlier in the inflammatory period of the radiation. In the article by Fowble *et al.* (31) the interval to exchange since RT was found to be significant when measured dichotomously. The odds of failure were 6.375 times higher among those patients with an interval of less than three months (compared to the group of more than 3 months). They didn't found any difference when the interval to exchange was measured in a continuous manner.

Aristei *et al.* (29) published a failure rate of 10% when the TTE was irradiated, whereas the rate was 27% when the irradiated element was the PI ($P = 0.239$). According to them, age emerged as a significant risk factor for prosthesis removal.

Cordeiro *et al.* (30) presented a paper in which the failure rate was 18.1% for the TTE group and 12.4% for the PI one. The difference was not statistically significant.

Interestingly, they reported that the prescribed energy for a total dose of 50–50.4 Gy (180–200 cGy per fraction) was 6 MV for the PI group and 15 MV photons for the TTE group in order to minimize the “scatter” dose off the magnetic TTE valve.

In their article, Fowble *et al.* (31) reported a global RF rate of 18%. The rate was 19.8% for the RT to TTE group and 7.7% for those patients in whom the irradiated implant was the PI. In univariate analysis they presented as the main risk factor for RF the absence of acellular dermal matrix (ADM) or serratus muscle coverage at the time of radiation. Failure occurred in 9.1% of patients when it was present versus 32.5% of patients when it wasn't ($P=0.0069$). For the group of women with full coverage, the location of the mastectomy scar was found to be a risk factor; with a failure rate of 19.2% when the scar was located at the inframammary fold in contrast with a 0% rate when other location was used. In the multivariate logistic regression analysis, weight was the most significant factor. They presented an OR for fail of 5.25 among those patients with a weight under 120 lb, compared with those of more than 120 lb ($P=0.0395$). They speculate that lower weight might be an important factor for interaction of thin skin flaps, absence of ADM or serratus coverage, short interval to exchange and inframammary scar. Contrary to this, some papers found high IBM as a predicting factor for failure (44). The authors also provide some variables in which a non-statistically significant association with an increased risk of RF was found: Diabetes, smoking, Nipple and areolar sparing mastectomies and hormonal/monoclonal treatments. They also mentioned an article (45) in which the use of chest wall RT boosts was found to be a significant failure predictor.

In the study by Yan *et al.* (32) a failure rate of 12.2% was found in the RT to TTE group compared with a 0.0% in the RT to PI cohort but the result was not statistically significant ($P=0.57$). In the article they point out some interesting references about the possible role of the inflation/deflation expander state when irradiating it on the RT to TTE group. A recent animal study (46) showed a higher epidermal atrophy, dermal inflammation, fibrosis and vascular changes when radiating deflated expanders in rabbits compared with those in which the expander was fully inflated. Recently, Woo *et al.* published a paper showing a statistically significant failure rate of 35% when deflated expanders were irradiated compared with a 6.9% rate when the radiation was applied to inflated expanders (47). Traditionally, it has been necessary to deflate, at least

partially, the expander prior to the RT in order to improve dosage of the target field. Nowadays radiation technology has improved enough that several articles have shown successful outcomes with the application of RT to fully inflated expanders (48,49).

According to Santosa *et al.* (33) timing of PMRT was not a significant predictor for failure. Their rate was 11.5% for the RT to TE group and 8.7% for the RT to PI one ($P=0.9$). They found older age and being a current or a former smoker to be significant predictors.

Ogita *et al.* (34) published a rate of 15.6% when radiating the TTE, versus a 10.2% when they radiated the PI ($P=0.54$).

The paper by Hvilsom *et al.* (50) was not included for meta-analysis as they compared results in both groups but in the setting of delayed reconstruction. Their results also showed and increased risk of failure when radiating the TTE.

Meta-analysis

The collected data from the ten studies are summarized in *Table 1*.

We performed a meta-analysis in two possible scenarios: a fixed-effect model and a random effect model (*Figure 2*). A high heterogeneity of $I^2=51\%$ was found ($P=0.03$). Thus, the random effect model is mainly considered. For the random effect model [*Figure 3*, meta-analysis (Random effect model)] the OR was 1.85, but the result was not statistically significant (0.96, 3.57; $P=0.067$). A size effect (z) of 1.83 was found. A sensitivity analysis is also performed (*Figure 4*). A significant OR of 2.32 would have been reached if we hadn't included the article by Aristei *et al.* Finally, a funnel plot is presented (*Figure 5*). A P value of 0.7345 was calculated for the linear regression test for funnel plot asymmetry. No publication bias exists.

Limitations of our paper include the fact that most of the papers collected for the meta-analysis presented retrospective data with a lack of patients recruited in a prospective and randomized approach. The definition of RF should be standardised to improve comparability between the studies.

Conclusions

There is a tendency towards a higher failure rate when the TTE is irradiated compared with the irradiation of the PI, but no strict statistical significance has been reached.

A deep understanding of complications risk versus

Table 1 Reconstructive failure

Author	Year	Total		Reconstructive failure		PMRT total	p
		PMRT to TE	PMRT to PI	PMRT Total	PMRT to PI		
Anderson	2009	62	12	3	0	74	0.21
Nava	2011	50	109	20	7	159	0.0001
Collier	2014	32	22	2	1	54	1
Lentz	2013	34	22	7	3	56	0.724
Aristei	2012	90	11	9	3	101	0.239
Cordeiro	2015	94	210	17	26	304	Unknown
Fowble	2015	86	13	17	1	99	Unknown
Yan	2016	41	11	5	0	52	0.57
Santosa	2016	104	46	12	4	150	0.9
Ogita	2018	32	49	5	5	81	0.54
Total		625	505	97	50	1130	

PMRT, postmastectomy radiation therapy; TE, tissue expander; PI, permanent implant.

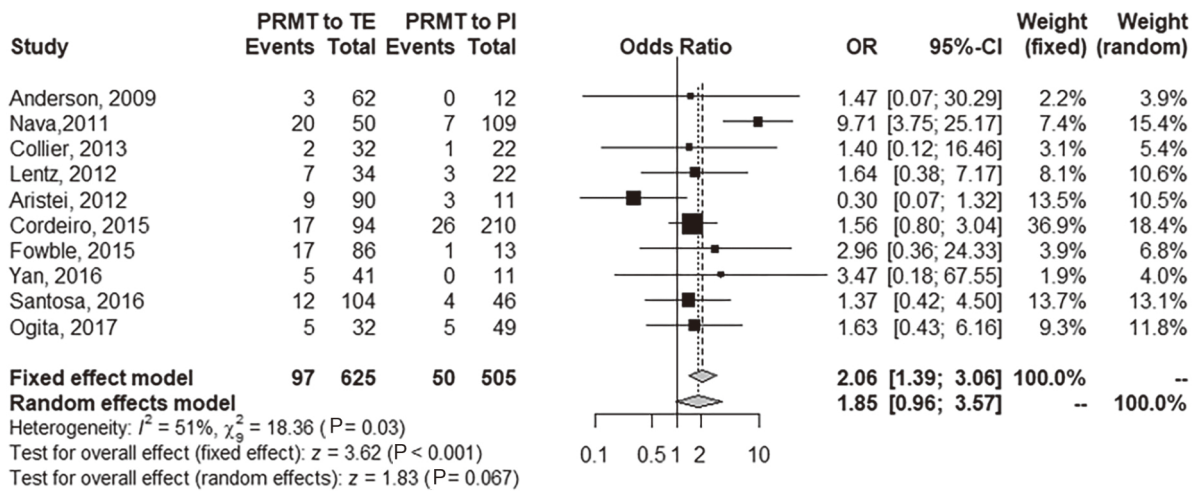


Figure 2 Meta-analysis: fixed and random effect models.

the potential benefits of immediate implant-based breast reconstruction is mandatory to improve the decision making process between the surgeon and the patients. In some women, the risk of complications may outweigh the benefit of this modality of reconstruction and thus, the predictive risk of failure should lead to avoid the combination of immediate reconstruction, implant-based approach and PMRT among them.

According to our literature review several factors could

act as risk predictors for failure of this reconstructive modality. Smoker patients, older ones, those with presence Low BMI/High BMI, diabetic women and patients with advanced tumours (N2-3/T1/those requiring adjuvant or neoadjuvant chemotherapy) might be at a higher risk. Some surgery related indicators may include: early exchanges (time from PMRT to TTE-PI exchange less than 3–6 months), nipple/areolar sparing mastectomies, inframammary fold incision, partial implant coverage.

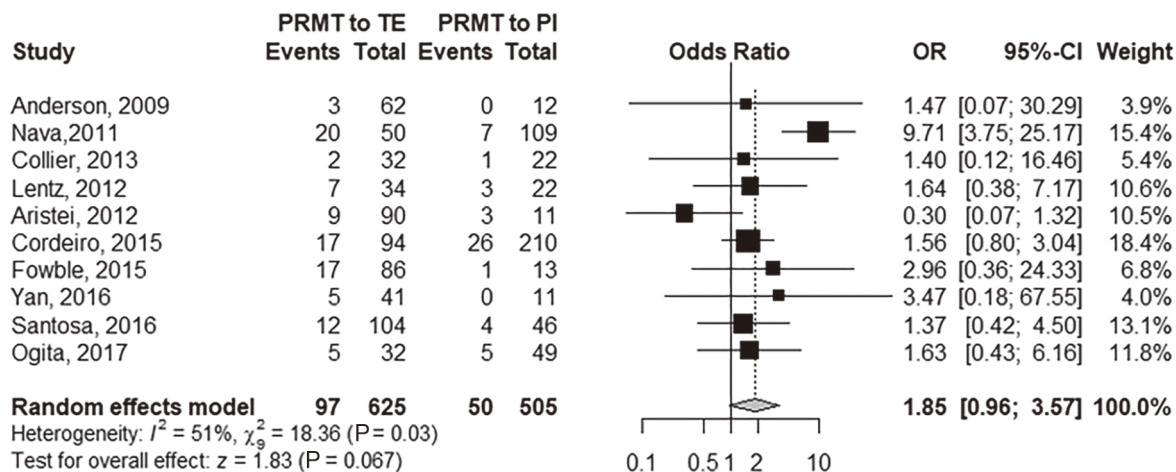


Figure 3 Meta-analysis (random effect model).

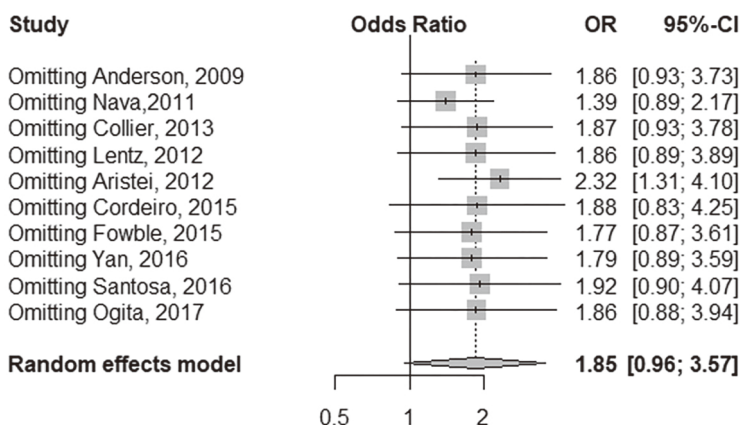


Figure 4 Sensitivity analysis (random effect model).

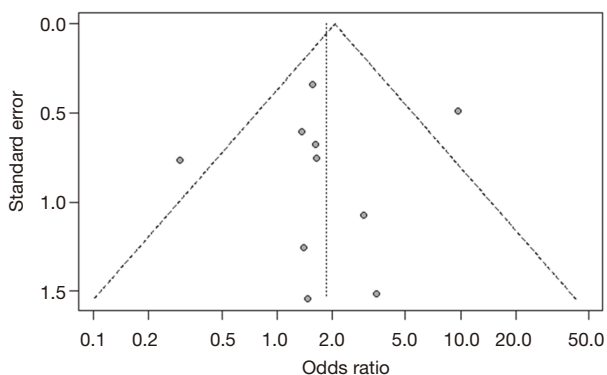


Figure 5 Funnel plot (random effect model).

Finally, some radiotherapy characteristics may also act as risk factors for RF: conventional RT (as compared with intensity modulated RT), high photons energy RT, deflated expanders at the time of RT, presence of chest wall RT Boost.

Further prospective and standardized studies trying to elucidate the influence of these suggested risk factors for outcome of RF have to be performed in order to establish a consensus about the indications and contraindications of this reconstructive modality. This will allow setting a protocol to help the surgeons to decide when to perform or delay an implant-based reconstruction and to individualize

the best PMRT timing approach for each patient.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/gs.2020.01.20>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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