Determining the outcomes of post mastectomy radiation therapy delivered to the definitive implant in patients undergoing one and two stage implant based breast reconstruction: A systematic review and meta-analysis.

Louise J Magill[1], Francis P Robertson[1], Gavin Jell[1], Ash Mosahebi[2] Mohammad Keshtgar[3].

1: Department of Surgery and Interventional Science, Royal Free Campus, University College London.

2: Department of Plastic and Reconstructive Surgery, Royal Free Hospital, London

3: Department of Breast Surgery, Royal Free Hospital, London.

Key words: Post Mastectomy Radiation Therapy; Breast Reconstruction; Implant Based Breast Reconstruction; Capsular Contracture; Failure.

Financial support: nil

Word count: 2376
Abstract word count: 228

Keywords: Breast reconstruction; Radiotherapy; Breast Cancer; Complications; Implant reconstruction; Cosmetic Outcome

Corresponding author:
Louise J Magill,
Division of Surgery and Interventional Science, Royal Free Campus, University College London,
9th Floor Royal Free Hospital,
Pond Street,
London,
NW3 2QG.
Email: louise.magill.14@ucl.ac.uk

Abstract

Background:

Post mastectomy radiation therapy is known to increase complication rate and implant loss in implant based breast reconstruction. The purpose of this study was to systematically review the literature regarding outcome of PMRT delivered to the permanent/definitive implant.

Methods:

Systematic review and meta-analysis of studies involving immediate implant based reconstruction and post mastectomy radiation therapy (PMRT) when delivered to the permanent implant.

Results:

Seven studies included 2921 patients (520 PMRT, 2401 control). PMRT was associated with significant increase in capsular contracture (7 studies, 2529 patients, 494 PMRT, 2035 control, OR 10.21 95% C.I 3.74 to 27.89, p<0.00001). In addition, PMRT was associated with a significant increase in revisional surgery (7 studies, 2921 patients, 520 PMRT, 2401 control, OR 2.18 95% C.I 1.33 to 3.57, p=0.002) and reconstructive failure (6 studies, 2814 patients, 496 PMRT, 2318 control, OR 2.52 95% C.I 1.48 to 4.29, p+o.ooo7). Moreover it was associated with a significant reduction in patient satisfaction (4 studies, 468 patients, 138 PMRT, 294 control, OR 0.29 95% C.I 0.15 to 0.57, p=0.0003) and cosmetic outcome (4 studies, 1317 patients, 238 PMRT, 1009 control, OR 28 95% C.I. 0.11 to 0.67, p=0.005)

Conclusions:

This meta-analysis demonstrates that within the first five years post implant-based reconstruction for those patients who receive PMRT, the rates of adverse events is

increased and there is significant reduction in patient satisfaction and cosmetic outcome.

Immediate two-stage breast reconstruction using a tissue expander followed by permanent implant is the most common form of breast reconstruction performed post mastectomy for breast cancer[1]. Implant based reconstruction following mastectomy can be performed immediately as a one (direct to permanent implant) or two stage procedure (tissue expander followed by permanent implant) or as a delayed procedure after several months. A key factor in the discussion around the optimal reconstructive pathway is based around the likelihood for the requirement of adjuvant radiotherapy as it has been associated with an increased risk of post-implant based reconstruction complications and implant loss. Since the publication of the Danish and Canadian trials in 1997, the numbers of patients eligible for post mastectomy radiotherapy are increasing [2, 3]. This is further supported by a subsequent study by Tendulkar et al. who reported a significant reduction (12%) in loco-regional recurrence in those patients receiving post mastectomy radiation therapy (PMRT) with only 1-3 positive axillary nodes[4].

It has been shown in some studies that PMRT negatively impacts on the cosmetic outcome and increases the complication rate for patients undergoing implant based reconstruction however the results are conflicting[5]. Delayed reconstruction or autologous reconstruction can be offered to women who are likely to undergo radiotherapy [6,7] However, delayed reconstruction following treatment with radiotherapy can often be much more technically challenging thus resulting in a poorer cosmetic result and leaves the patient without a breast for a period of time[8]. Offering immediate implant-based reconstruction provides replacement of the breast mound as well as significant psychological and emotional advantages for the patient [9]. There are various advantages of implant-based over autologous reconstruction

including reduced operative time, avoidance of donor site morbidity, reduced cost and can be offered to those patients unsuitable for autologous reconstruction either due to co-morbidities or lack of available donor tissue[10].

In the two-stage setting of implant based breast reconstruction, radiotherapy can be given at one of three time-points, firstly to the un-expanded tissue expander, secondly to the fully expanded tissue expander prior to exchange to a permanent implant and lastly following implant exchange radiotherapy can be delivered to the permanent implant. In one stage implant reconstruction, radiation is delivered to the permanent implant.

To date, studies investigating the effect of PMRT on implant based reconstruction including one and two stage reconstructions are limited to mostly single unit, retrospective cohort studies. Moreover, research is limited by diverse treatment regimes regarding the timing of radiotherapy often dictated by local hospital protocols or advisory boards (radiation therapy delivered to tissue expander or permanent implant or delivered pre or post mastectomy) which incurs significant bias as operating on previously irradiated tissue is associated with a more complex procedure and an increased risk of post-operative complications. In addition, small patient sample size and lack of control population results in variable outcomes. Therefore a meta-analysis of these trials is of use as combining underpowered studies may identify significant results.

A recent meta-analysis of implant based breast reconstruction showed that in patients undergoing nipple-sparing mastectomy the complication rate was comparable and

cost was lower for patients having one stage implant reconstruction compared to two stage [11].

Within the current scientific literature there is no other meta-analysis investigating the impact of PMRT on to the permanent breast implant in patients undergoing one and two-stage implant based breast reconstruction.

Aim:

The aim of this review was to systematically examine the effect of post mastectomy radiation therapy delivered to the permanent implant to determine the incidence of complications such as implant loss, capsular contracture and patient satisfaction to determine the impact of post mastectomy radiation therapy to permanent breast implants.

Methods:

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12] (Figure 1). The study protocol was registered with the University of York Centre for Reviews and Dissemination international prospective register of systematic review (2015:CRD42015026061). Ovid MEDLINE and Embase databases were searched up to and including the second week of October 14th 2016 using the search terms ‘ breast reconstruction and or breast implant medical literature was searched for studies comparing patients receiving radiotherapy post mastectomy directly to permanent implant. Patients undergoing delayed reconstruction post mastectomy, combined autologous reconstruction, radiation delivered to the tissue expander prior to implant exchange for the permanent implant and patients with a prior history of radiotherapy were excluded. Primary outcomes were implant loss, capsular contracture and revisional surgery. Secondary outcomes were cosmesis and patient satisfaction.

MEDLINE and Embase databases were searched up to and including the second week of October 2016 using the following search algorithm: ((breast reconstruction.mp. or Mammaplasty/) OR ((breast$ adj3 (reconstruction or implant)).mp.)) AND ((Radiotherapy, High-Energy/ or Radiotherapy, Intensity-Modulated/ or Radiotherapy/ or Radiotherapy, Computer-Assisted/ or Radiotherapy, Image-Guided/ or Radiotherapy, Adjuvant/ or Radiotherapy Dosage/) OR (radiotherapy.mp. or Radiotherapy/))

A manual search was also performed to search for relevant studies. Publications were excluded if not relevant to the topic, review articles, autologous breast reconstruction articles, letters, comments and conference abstracts.

All patients undergoing immediate one or two stage implant breast reconstruction were included in the study. Articles had to define that PMRT was delivered to the permanent implant or following tissue expander exchange to the definitive implant to be included. Patients who received PMRT to the tissue expander prior to exchange to PI and those patients who had combined implant autologous or autologous breast reconstruction were excluded. A time limit of the studies published in the last 20 years was chosen to reflect the improvements in breast implant technology and design as well as improvements in surgical and radiation techniques to limit bias.

Primary outcomes were defined as capsular contracture (as defined as Baker Grade III or IV), revisional surgery and reconstructive failure (as defined as removal or replacement of the implant).

Secondary outcomes were defined as patient satisfaction and cosmetic outcomes. Patient satisfaction outcomes varied between studies and a good outcome was accepted as ‘partially to fully satisfied’, ‘medium to good’ and ‘satisfied’ for the purpose of our review. Cosmetic outcomes were similarly varied but defined by the operating surgeon.

Statistical Analysis

All primary and secondary endpoints were entered into and analysed using Revman 5® software (The Nordic Cochrane Centre, Copenhagen, Denmark) using a random effects DerSimonian-Laird model and results were reported with 95% confidence

intervals. Heterogeneity was assessed using τ^2, χ^2, and I^2 measures and was deemed significant if $p<0.10$ or I^2 was greater than 30%.

Results:

A total of 2 979 results were identified from combined Ovid Medline and Embase searches. Following electronic removal of duplicates, 2 277 remained. Following review of the title and abstracts 1887 studies were considered irrelevant, 224 were reviews, case reports, letters and editorials, 48 were autologous breast reconstruction and radiation therapy and 12 were outside the defined time frame. 110 studies were selected for full text review, 50 described radiation therapy to tissue expander or combined outcomes of TE/PI and/or autologous reconstruction, 10 did not address surgical outcomes of radiation therapy, 33 were conference abstracts, 4 studies did not report outcomes for non-irradiated patients, 2 studies reported on less than 5 patients, 2 studies contained duplicate patient populations and 2 studies were not available in full text. Thus, seven studies[13, 14, 15, 16, 17, 18, 19] were selected for data extraction and inclusion in the final analysis containing 2921 patients (520 PMRT, 2401 control).

Primary End Points:

All seven studies commented on capsular contracture[13, 14, 15, 16, 17, 18, 19] (2529 patients: 494 PMRT, 2035 control). There was significant increase in rate of capsular contracture in those patients receiving PMRT (OR 10.21, 95% C.I 3.74 to 27.89, $p<0.00001$). However, there was significant heterogeneity between the studies (I^2=88%, $p<0.00001$) indicative of retrospective cohort studies (Figure 2)

In addition, all studies reported patients undergoing revisional surgery including those with reconstructive failure[13, 14, 15, 16, 17, 18, 19] (7 studies, 2921 patients: 520 PMRT, 2401 control) (Figure 3). There was no significant heterogeneity between the studies

(I^2=30%, p=0.20). There was a significant increase in numbers of patients undergoing revisional surgery in the PMRT group (OR 2.18, 95% C.I 1.33 to 3.57, p=0.002).

Six studies[14, 15, 16, 17, 18, 19] (2814 patients: 496 PMRT, 2318 control) described reconstructive failure (as defined as implant removal or replacement) (Figure 4). There was no significant heterogeneity between the studies (I^2=21%, p=0.28). PMRT was significantly associated with an increased number of patients with reconstructive failure (OR 2.52, 95% C.I 1.48 to 4.29, p=0.0007)

Secondary End points:

Four studies reported patient satisfaction outcomes[15, 16, 18, 19] (468 patients: 174 PMRT, 294 control). There was no significant heterogeneity between the studies (I^2=0%, p=0.5). There was significant reduction in patient satisfaction rates in patients undergoing PMRT compared to the control group (OR 0.29 95% C.I 0.15 to 0.57, p=0.0003) (Figure 5).

Four studies reported cosmetic outcome[14, 16, 18, 19] (1317 patients: 275 PMRT, 1042 control). There was significant heterogeneity in the studies (I^2=59%, p=0.09) with a significant reduction in acceptable cosmetic outcome in patients undergoing PMRT compared to the control group (OR 0.28 95% C.I 0.11 to 0.67, p=0.005) (Figure 6).

Discussion:

Radiotherapy has now been shown to be increasing efficacious in early stage breast cancer disease as well as those with established disease. With an increasingly younger population of patients diagnosed with breast cancer, the numbers of patients undergoing implant based breast reconstruction and PMRT is set to increase. Implant based breast reconstruction is the most popular form of reconstruction and may represent increasing numbers of younger patients who lack the adipose reserves to perform autologous reconstruction or the patients desire to achieve a more aesthetically pleasing, non-ptotic breast. To date, studies on PMRT and permanent implants are limited due to their small patient sample size, retrospective nature, lack of randomisation and often lack of control groups to compare their findings – therefore a systematic review of this topic is important as it may demonstrate significant results from underpowered studies.

Moreover, the timing of delivery of radiation during two-stage implant reconstruction process varies between units with many centres completing radiation therapy before exchange of TE to the definitive implant or in those patients who undergo a course of chemotherapy prior to radiotherapy treatment. In addition, there remains significant heterogeneity in the reporting of surgical outcomes often without including patient satisfaction that makes it difficult to assimilate the full true impact of delivered to the definite implant – as such this review has focused on patients undergoing PMRT to the permanent implant and not to temporary tissue expanders.

The results from this review demonstrate clearly that the deliverance of PMRT to a permanent implant is associated with significantly increased rate of capsular contracture. The incidence of capsular contracture increased from 5% in the control group to 43% in patients undergoing PMRT.

Furthermore these patient groups are more likely to suffer from a failure of their reconstructive surgery (9% vs. 6%, $p<0.001$) and to have to undergo further revisional surgery (11% vs. 5%, $p=0.002$).

Cosmetic outcome as reported by both patients and surgeons were significantly poorer in patients undergoing PMRT.

There are limitations to this review. There was significant heterogeneity in the method that each paper reported their outcomes. We included 'partially to fully satisfied'[15], 'medium to good'[16] and 'satisfied'[18, 19] as acceptable patient satisfaction outcomes for the purpose of our review. In addition, this was echoed in the reported outcomes for cosmesis[14, 16, 18, 19].

Radiotherapy was generally delivered 3-6 weeks following reconstructive procedure, however in a study published by Vandemeyer et al. two patients included in the study with permanent implants were irradiated for local recurrences months after reconstructive surgery[15]. In addition, in a study reported by Cordeiro et al. those patients receiving PMRT to permanent implant had already undergone post mastectomy chemotherapy in comparison to those patients in the same study who did not require chemotherapy and had therefore PMRT delivered to the tissue expander [14]. This may therefore select a patient cohort with later stage disease requiring several adjuvant treatment modalities that may influence their overall quality of life and may impact on their psychological state and patient satisfaction scores. However, despite this, data published by Cordeiro et al. 2015 reported no difference in patient satisfaction scores between the PMRT to tissue expander and PMRT to permanent implant groups [14]

All studies stated that textured implants were employed, one study used only saline-filled implants[13] another study stated that eight of 12 patients underwent reconstruction with saline implants, the remaining patients having silicone breast implants and one study stated only 'textured' implants[15].

In addition, a study by Benediktsson et al. excluded 14 patients who had lost their implant before the two year follow up therefore this will have led to under-reporting the revisional surgery and reconstructive failure data[13] . Moreover, 6 patients in the study did not undergo revisional surgery due to personal choice or advanced disease which may have influenced the results[13]

In the study by Cordeiro 2015, not all patients in the study had capsular contracture outcomes recorded which might have led to bias in the results.

Interestingly, a study by McCarthy et al. reported outcomes for those patients undergoing bilateral reconstruction with unilateral radiotherapy using the non-irradiated breast as a control[19]. All patients described their cosmetic outcome as excellent/very good or good but only 70% of patients were satisfied with their reconstruction[19].

The average length of follow up in these studies was 31 months (range 9 – 65 months). There were a significant number of patients lost to follow up by five years in one study[13] therefore we used the data generated at 2 years follow up for the purpose of our review. No study followed patients up beyond five years and therefore the long-term outcome has not yet been reported.

Conclusion

This meta-analysis has shown that there are significantly increased rates of capsular contracture, revisional surgery and reconstructive failure as well as reduced patient satisfaction scores and cosmetic outcome in those patients receiving PMRT to a permanent implant within the first five years of surgery. As this is the first meta-analysis to report patient outcomes for PMRT delivered to the permanent implant, it provides robust knowledge which can help guide informed decision making when deciding the most appropriate method of breast reconstruction for the patient undergoing PMRT. Further long-term follow-up to determine the long-term complication rates of PMRT are required.

Conflict of Interest: nil

Funding: nil

References

1. Albornoz CR, Bach PB, Mehrara BJ et al. A paradigm shift in the U.S. Breast Reconstruction: increasing implant rates. *Plast Reconstr Surg* 2013; **131:** 15-23.
2. 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.
3. 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.
4. Tendulkar RD, Rehman S, Shukla ME, Reddy CA, Moore H, Budd GT et al. Impact of postmastectomy radiation on locoregional recurrence in breast cancer patients with 1-3 positive lymph nodes treated with modern systemic therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; **83**: e577–81.
5. Berbers J, van Baardwijk A, Houben R, Heuts E, Smidt M, Keymeulen K et al. 'Reconstruction: before or after postmastectomy radiotherapy?' A systematic review of the literature. *Eur. J. Cancer* 2014; **50:**2752–62.
6. Korwar V, Skillman J, Matey P. Skin reducing mastectomy and immediate reconstruction: the effect of radiotherapy on complications and patient reported outcomes. *Eur. J. Surg. Oncol.* 2014; **40**: 442–8.
7. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. *Breast Cancer Res. Treat.* 2011; **127**: 15–22 (2011).
8. Chevray PM. Timing of breast reconstruction: immediate versus delayed. *Cancer J.* 2008; **14**: 223–9
9. Atisha D, Alderman AK, Lowery JC, Kuhn LE, Davis J, Wilkins EG. Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the Michigan Breast Reconstruction Outcomes. *Ann Surg.* 2008; **247**: 1019-28.
10. Chawla AK, Kachnic LA, Taghian AG, Niemierko A, Zapton DT, Powell SN. Radiotherapy and breast reconstruction: complications and cosmesis with TRAM versus tissue expander/implant. *Int. J. Radiat. Oncol.* 2002; **54**: 520–526.
11. Lee KT, Mun GH. Comparison of one-stage vs two-stage prosthesis-based breast reconstruction: a systematic review and meta-analysis. *Am. J. Surg.* 2015; **212**: 336-44.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: 2535.
13. Benediktsson K, Perbeck L. Capsular contracture around saline-filled and textured subcutaneously-placed implants in irradiated and non-irradiated breast cancer patients: five years of monitoring of a prospective trial. *J Plast Reconst Aesthet Surg.* 2006; **59**: 27-34
14. Cordeiro PG, Albornoz CR, McCormick B, Hudis CA, Hu Q, Heerdt A, Matros E. What Is the Optimum Timing of Postmastectomy Radiotherapy in

Two-Stage Prosthetic Reconstruction: Radiation to the Tissue Expander or Permanent Implant? *Plast. Reconstr. Surg.* 2015; **135**: 1509–17.

15. Vandeweyer E, Deraemaecker R. Radiation therapy after immediate breast reconstruction with implants. *Plast. Reconstr. Surg.* 2000; **106**: 56–8.
16. Nava MB, Pennati AE, Lozza L, Spano A, Zambetti M Catanuto G. Outcome of different timings of radiotherapy in implant-based breast reconstructions. *Plast. Reconstr. Surg.* 2011; **128**: 353–9.
17. Rella L, Telegrafo M, Nardone A, Miella A, Stabile Ianora AA, Lioce M, Angelelli G, Moschetta M. MRI evaluation of post-mastectomy irradiated breast implants: prevalence and analysis of complications. *Clin. Radiol.* 2015; **70**: 948–53.
18. Cordeiro PG, Pusic AL, Disa JJ, McCormick B, VanZee K. Irradiation after immediate tissue expander/implant breast reconstruction: outcomes, complications, aesthetic results, and satisfaction among 156 patients. *Plast. Reconstr. Surg.* 2004; **113**: 877–81.
19. McCarthy CM, Pusic AL, Disa JJ, McCormick BL, Montgomery LL, Cordeiro PG. Unilateral postoperative chest wall radiotherapy in bilateral tissue expander/implant reconstruction patients: a prospective outcomes analysis. *Plast. Reconstr. Surg.* 2005; **116**: 1642–7.

Fig 1: PRISMA flow chart.

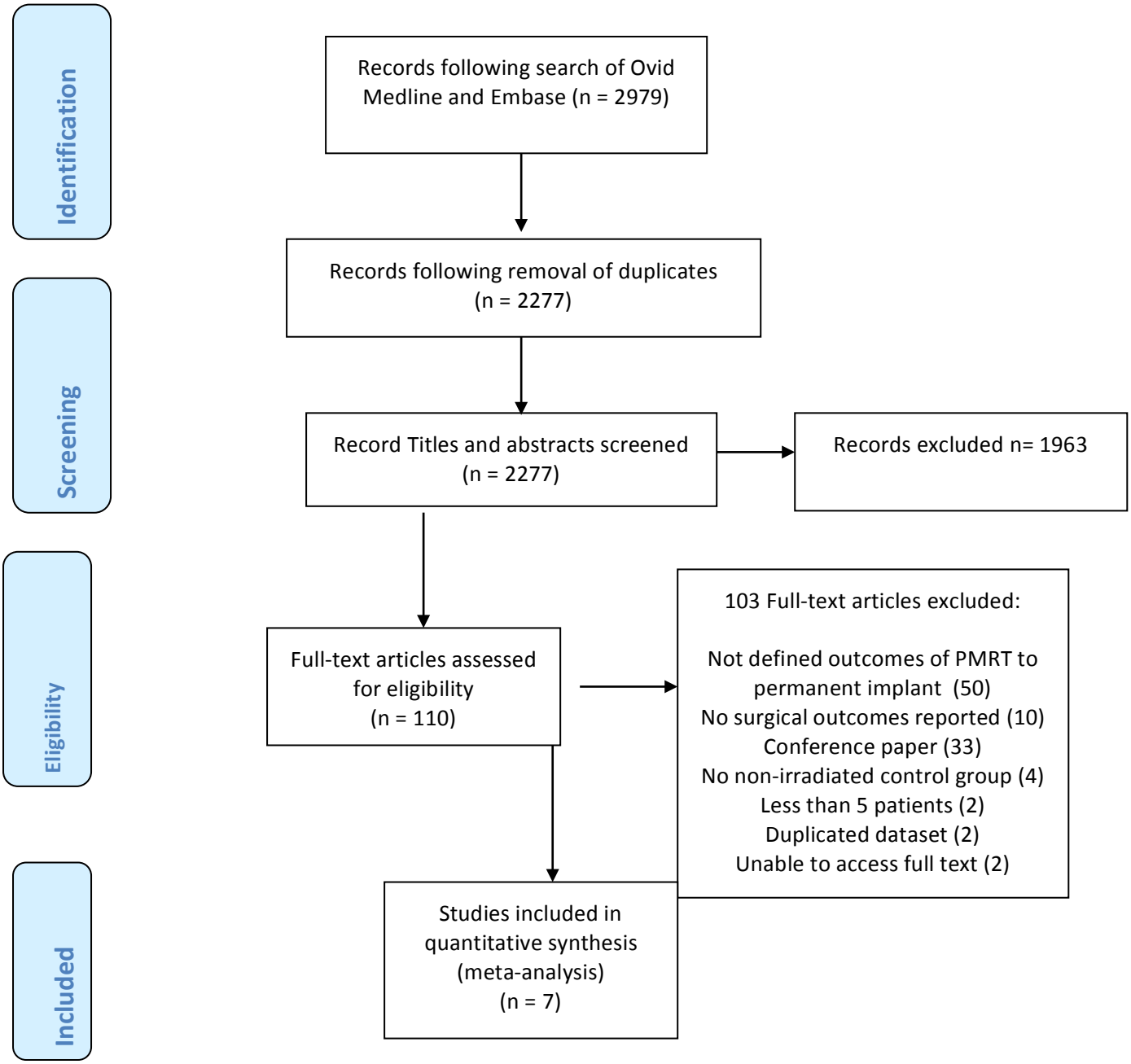

Figure 2: Forest plot demonstrating increased incidence of capsular contracture in patients undergoing PMRT

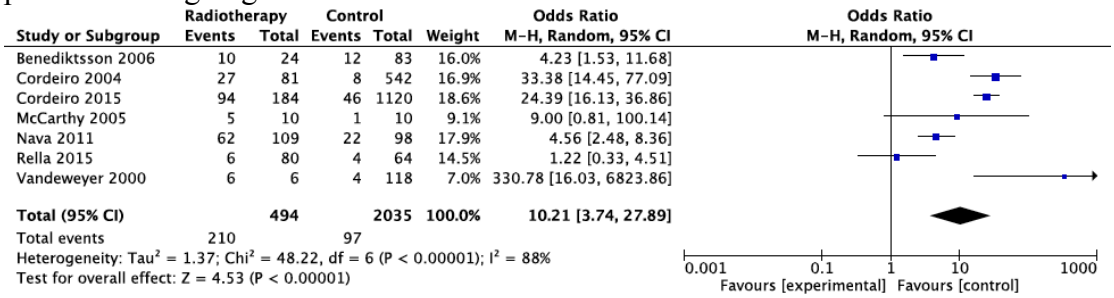

Figure 3: Forest plot demonstrating increased incidence of revisional surgery in patients undergoing PMRT

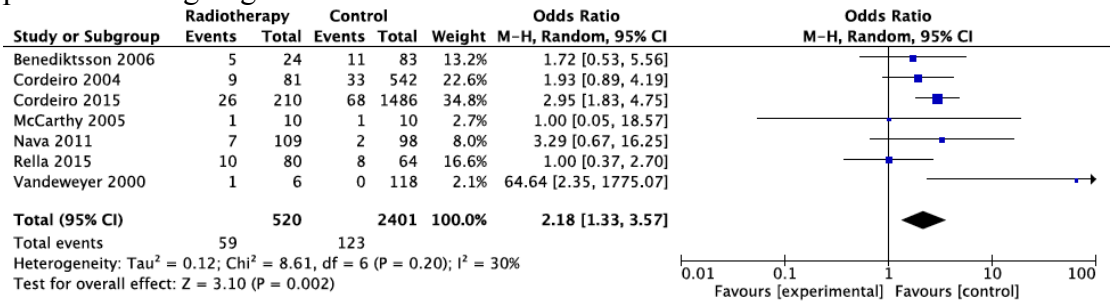

Figure 4: Forest plot demonstrating increased incidence of reconstructive failure in patients undergoing PMRT

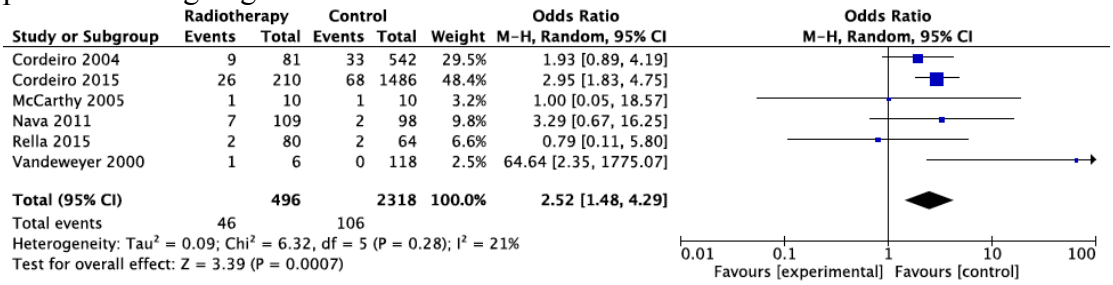

Figure 5: Forest plot demonstrating a reduction in patient satisfaction at reconstructive outcome following PMRT

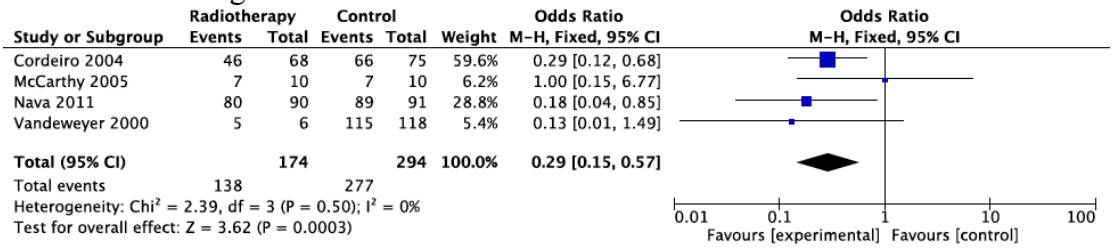

Figure 6: Forest plot demonstrating reduced cosmetic outcome as reported by the surgeons in patients undergoing PMRT