

Cost-Effectiveness of the Biozorb Device for Radiation Planning in Oncoplastic Surgery

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Abstract

Purpose:

With the extent of breast tissue manipulation using oncoplastic surgical techniques, there lies a challenge in marking the tumor bed for adjuvant radiation therapy planning. Two competing techniques in doing so exist and involve the traditional placement of surgical clips in the surgical tumor bed or the newer technique of placing a Biozorb marker in the tumor bed. Our goal was to perform a cost-utility assessment to see which tumor bed marking approach is more cost-effective. Based on device list prices and clinical outcomes from a comprehensive literature review, we assessed if an approach either dominated or had an incremental cost-utility ratio of less than \$50,000/QALY since either would signify cost-effectiveness.

Results:

From a cost comparison, the Biozorb marker (\$1250) was far costlier than the clip applicator device (\$50). Our PRISMA search (Figure 1) reviewed 133 articles for clip placement and 42 articles for Biozorb placement in oncoplastic surgery with 2 clip placement articles and 3 Biozorb articles meeting criteria. The available data for either marking technique suggests reasonable tumor bed identification for adjuvant radiation treatment without clear clinical advantages supporting one technique over the other. Overall clinical equivalence in the setting of a clear cost advantage suggests dominant cost-effectiveness in favor of clips.

Conclusion:

Using surgical clips to identify the tumor bed in oncoplastic surgery is dominant and more cost-effective over the Biozorb technique as clips are relatively inexpensive while both techniques reasonably identify the tumor bed.

Keywords: Biozorb, cost-effectiveness, oncoplastics, radiation planning, surgical clips

1. Introduction

Oncoplastic surgery has gained traction over the last few years as it allows patients to retain a natural appearance following large oncological procedures. The field has established several techniques as its hallmark procedures, which include a variety of mastopexy approaches and reduction mammoplasty techniques (Chatterjee et al., 2017; Masetti et al., 2006; Piper, et al., 2015; Berry et al., 2010). Although cosmetic outcome is a focus of these procedures, the primary indication for the surgery is removal of a tumor. Thus, understanding the impact of these surgeries on oncological treatment is important. In particular, their effect on surgical cavity location is important as it directly informs and directs post-op boost radiation. The large parenchymal shifts resulting from various oncoplastic surgeries make it challenging to assess the tumor bed location without assistance. A couple of studies to date have quantified the large tissue shifts post-oncoplastic surgery to validate the need for a definitive way to define the tumor bed following these surgeries (Kirova et al., 2011; Alco et al., 2016; Eaton et al., 2014).

Historically, imaging modalities, particularly CT scans, have been used to plan for boost radiation therapy following surgery. However, several studies have shown their inconsistency in providing accurate tumor bed coordinates for a variety of reasons, including user variability and variances in patient tissue density and size, and difficulties of visualization due to seroma formation (Bates et al., 2007; Metcalfe et al., 2013; Messer, et al.,

1997; Den et al., 2014; Boersma et al., 2012; Landis, 2007). Over the years, a variety of other tumor marker methods were tried and tested, including embolization coils and a variety of surgical clips (Braeuning et al., 2000). To date, surgical clips have become recognized as the gold standard for tumor bed identification. Many studies have shown their effectiveness in accurately localizing the target volume for radiation purposes, as they have shown to have minimal movement and are easily identifiable on various image modalities (Landis, 2007; Petersen, 2007; Hartough et al., 2011; Oh, 2006; Denham et al., 1991; Bedwinek, 1993; Youn et al., 2015; Weed et al., 2004; Harrington et al., 1996; Penninkhof et al., 2009). Despite the abundance of literature proving their effectiveness, there still remains little literature to date on their use and effectiveness in oncological procedures.

Focal Therapeutics, a medical device company based in Aliso Viejo, CA introduced a novel tumor marker, Biozorb, to the market. It is a 3D implantable device consisting of a framework of six titanium marker clips designed to facilitate identification of the surgical cavity post-op. A study performed by Ward et al. exhibited Biozorb's presence on a variety of imaging modalities, including mammography, ultrasound, MRI, chest radiography, and CT in an effort to increase awareness over its form and appearance (Ward et al., 2018). A more recent study by Wiens et al. demonstrated the device's ability to reduce clinical target volume and planning target volume of boost radiation post-op with statistically significant results (Wiens et al., 2018). However, the authors noted no difference in the ability of the device to reduce radiation to secondary organs, in fact noted an increase in ipsilateral lung radiation. To date, there have been limited studies evaluating the effectiveness of this device in properly marking the tumor cavity, as it is a fairly new device.

The primary purpose of this study was to evaluate these two competing techniques, the traditional placement of surgical clips in the surgical tumor bed and the placement of the Biozorb marker in the tumor bed in the context of oncological surgery. A comprehensive literature review was undertaken to compare the reported clinical effectiveness of both techniques. A cost comparison analysis was then performed to inform readers of the cost effectiveness of using one marking technique over the other to better inform surgeon decisions.

2. Methods

2.1 Assessing Clinical Outcomes

In order to assess the clinical outcomes of the two marking techniques, we began by performing a systematic literature review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, shown in Figure 1. Eligible studies included studies evaluating the use of surgical clips and the Biozorb device in the context of oncological surgery. Exclusion criteria included studies with no discussion of these interventions in the context of oncological surgery.

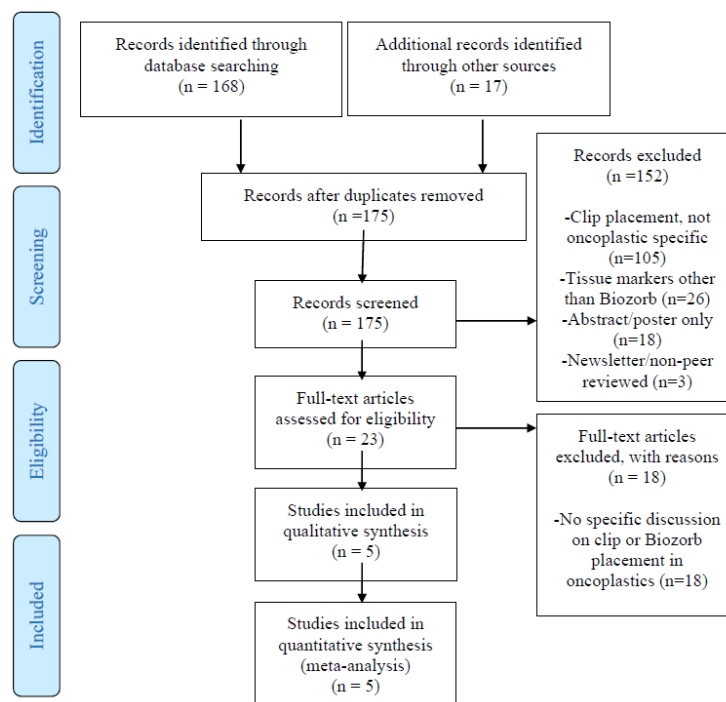


Figure 1. PRISMA 2009 Flowchart for Literature Search on Surgical Clip & Biozorb Placement in Oncological Surgery

We searched PubMed and Embase (Ovid) from the inception of each database through February 2018, with the last literature search performed on August 1st, 2018. The search was conducted using the following keywords: “oncoplastic” and “tumor bed identification.” To ensure identification of all relevant articles, other additional controlled vocabulary terms (I.e. MeSH terms in PubMed and Emtree terms in Embase) and keywords were used. Search results were then manually reviewed to assess articles specifically discussing Biozorb or surgical clips as the identification methods in oncoplastic surgery.

Two authors (RR, KH) reviewed search results and performed a title and abstract review to evaluate studies for inclusion and exclusion, with disagreements resolved by a third author (AC). Studies meeting inclusion criteria were oncoplastic studies of intraoperative clip or Biozorb placement in defining tumor bed in North America or Europe. Exclusion criteria were as follows: studies evaluating marking modalities other than surgical clips or Biozorb, and non-oncoplastic papers. We also excluded papers not published in American or European journals. We then reviewed the references therein to identify other relevant articles not identified by the original bibliographic search to ensure capture of all relevant articles.

A total of 175 articles were reviewed, 168 from the database search and 17 manually from additional sources.

2.2 Assessing Cost

A relatively simple cost comparison was performed involving the direct costs of both medical devices. Given that the oncoplastic operation would involve a similar type of local tissue rearrangement and breast remodeling regardless of the choice of device, it was reasonable to assume that other indirect and direct costs were the same. Therefore, the cost of a clip applier device was found to be \$50, and the list price of the Biozorb device was found to be \$1,250, with no other cost differences noted between operations.

2.3 Assessing Clinical Outcomes

Our clinical outcomes analysis was based off evidence in present literature depicting how well Biozorb or surgical clips performed in marking a tumor bed. In review of the literature, we hoped to attempt to analyze other clinical outcome parameters such as aesthetics, but could only do this if there was reasonable comparison data on aesthetics comparing Biozorb with surgical clips with reasonable scientific method. Anecdotal statements in presentations or simple case reports were not included.

2.4 Assessing Dominant Strategy versus Using Incremental Cost-Utility Ratio (ICUR)

Assuming there is reasonable clinical outcomes data comparing both competing techniques, the next step in cost-utility analysis would be to assess a dominant strategy, if it exists, or to create a decision analytic model evaluating the 2 marking strategies: surgical clips vs. Biozorb if no dominance exists. Central to assessing which device is cost-effective is the use of the incremental cost–utility ratio (ICUR) depicted below:

$$ICUR = ((\text{Expected cost of standard intervention}) - (\text{Expected cost of competing intervention})) / ((\text{Expected QALY of standard intervention}) - (\text{Expected QALY of competing intervention}))$$

$$ICUR = ((\text{Expected cost of surgical clips}) - (\text{Expected cost of Biozorb})) / ((\text{Expected QALY of surgical clips}) - (\text{Expected QALY of Biozorb}))$$

An intervention is deemed “dominant” (and hence cost-effective) if:

1. It has better or equivalent clinical outcome to its competing intervention and is less costly. Dominance with regards to the ICUR is depicted as a negative value or a value approaching infinity (Dukhovny, 2011)

An intervention was deemed “cost effective” if the ICUR is greater than 0 and less than the “willingness to pay” (WTP), for an added year of health. While some studies argue for much higher valuation for added years of life, the majority of studies to date have deemed the WTP to \$50,000 based on prior studies (Grosse, 2008)(Neumann, Cohen, Weinstein, 2014)(Ubel, Hirth, Chernew, Fendrick, 2003)(Chatterjee et al., 2013)(Chatterjee, 2016)(Asban et al., 2018). If one marking technique is more clinically effective and costs less, then this strategy, by definition dominates as the superior strategy, making it unnecessary to calculate the ICUR (Drummond, 2005).

3. Results

3.1 Literature Review and Clinical Outcomes Results

The comprehensive systematic literature review yielded a total of 5 article which satisfied all inclusion and exclusion criteria, 3 discussing Biozorb and 2 discussing traditional surgical clips in oncoplastic surgery (Table 1). The five articles pooled a total of 359 patients undergoing oncoplastic surgery with either surgical clips or the Biozorb device as the marking method for post-op boost radiation planning.

Table 1. Final Included Studies

Authors	Number of Oncoplastic Patients	Marker Type Studied	Aesthetic Advantage Studied	Author Final Recommendations
Pezner et al. 2013*	25	Surgical clips	No	Use 6-10 surgical clips to effectively mark the tumor bed
Furet et al. 2014*	18	Surgical clips	No	Use 3 or more clips to effectively mark the tumor bed
Cross et al. 2014*	65	Biozorb	No	Device was effective in marking the tumor bed
Cross et al. 2017*	108	Biozorb	No	Device was effective in marking the tumor bed
Wiens et al. 2018*	143	Biozorb	No	Device was effective in marking the tumor bed

*34, 35, 36, 37, 25 (in order as shown in table)

3.2 Incremental Cost-Utility Ratio (ICUR) and Dominance

Given that surgical clips were substantially less expensive than Biozorb (\$50 versus \$1250), there would need to be a clinical benefit offered by Biozorb in order to justify the cost. Our literature review showed little clinical data noting any advantage favoring the Biozorb device over standard practice being the surgical clip placement. Both interventions appeared to mark the tumor cavity effectively per our findings listed in Table 1. Other clinical outcomes such as pain and infection were difficult to compare as there was little head to head comparison. From a cavity marking perspective, there were reports noted by Furet et al. and Pezner et al. noting tumor bed shifts with fewer clips (Pezner et al., 2013; Furet et al., 2014). This seemed to improve if there were more clips placed. Additionally, the concept of “migration” of surgical clips is less likely with surgical clips placed rather than radiological clip markers given the physical placement and capture of tissue when fixating the clip surgically in the operating room. While pain and discomfort have been noted with the Biozorb device, without having a comparison with clips, it is difficult to fault the device versus the surgery performed (and possible subsequent radiation). It was notable that Wiens et al. showed a statistically significant increase in the amount of radiation to the ipsilateral lung in the Biozorb arm compared to the traditional surgical clips arm but the long-term impact of this clinically is unknown (Wiens et al., 2018). Thus, clinical outcomes outside the cavity marking abilities of both interventions could not reliably occur given the scarce presence of peer reviewed, reasonable scientific data directly comparing each approach.

Table 2. Final Included Studies: Reported Post-Op Complications

Authors	Reported Complications
Pezner et al. 2013*	Tumor bed shift with less than 4 clips
Furet et al. 2014*	Post-op intersection between clips and initial tumor site decreased with fewer clips
Cross et al. 2014*	None reported
Cross et al. 2017*	Pain/Discomfort: 1/108 (0.9%) Erythema: 1/108 (0.9%) Infection: 0/108 (0%) Re-excision for positive margins: 13/108 (12.4%)
Wiens et al. 2018*	Secondary Organ Radiation: Mean Gy heart (left sided), Biozorb vs. traditional clips= 2.24, 2.18 Mean Gy ipsilateral lung mean, Biozorb vs. traditional clips =7.72, 7.53 V ipsilateral lung receiving 20Gy mean, Biozorb vs. traditional clips= 13.7, 11.1

*34, 35, 36, 37, 25 (in order as shown in table)

Given this, the clinical outcome comparing surgical clips to Biozorb based on their ability to mark the cavity should be noted to be equivalent. Therefore, with the cost difference advantage of \$1200 favoring surgical clips and an equivalent clinical outcome between both interventions, the ICUR quotient becomes infinity (-\$1200/0) noting surgical clips to be a dominant choice over Biozorb.

4. Discussion

The results from our comprehensive literature search highlight the shortage of data comparing clinical benefit of

both tumor bed marking techniques in the context of oncoplastic surgery. The lack of comparative literature makes it difficult to make a sound clinical judgment favoring the newer and more expensive Biozorb technique, and the need to show clinical benefit on Biozorb's behalf is essential if it is to be adopted as the newer tumor bed marking device over the standard (and much less expensive) surgical clips option. In sum, our results show that traditional surgical clips, in the absence of comparative data proving superior clinical benefit of Biozorb, is less costly and more cost-effective for healthcare resources for marking the breast tumor bed in the setting of oncoplastic surgery.

A cost-utility analysis is commonly used to determine the cost of particular interventions in terms of their utility, which includes quantity needed over a lifetime as well as quality of life. It has been used in a variety of surgical studies to date and have helped inform surgeon decisions (Chatterjee et al., 2015; Chatterjee et al., 2015; Chatterjee et al., 2014; Chatterjee et al., 2015; Fischer et al., 2016; Krishnan et al., 2016; Krishnan et al., 2015; Krishnan et al., 2014; Offodile et al., 2015; Thoma et al., 2012; Shekter et al., 2018). Such a technique allows for identification of interventions with the best clinical outcomes and best value, which is especially important with the large healthcare costs associated with breast oncology management (Lang et al., 2014; Bekelman et al., 2014). The results of our study underscore the importance of assessing the value of a newer intervention before widespread adoption. When oncoplastic surgery is performed, the aesthetic advantages incurred by the local tissue rearrangement have long been documented and are well established without the use of Biozorb (Chatterjee et al., 2017; Silverstein et al., 2014; Clough et al., 2010; Anderson et al., 2005; Kelsall et al., 2017). However, Biozorb has been reported to have capabilities in marking the newly created tumor bed after an oncoplastic resection and reconstruction. Our PRISMA literature review has shown data that verifies Biozorb's ability in the marking of the cavity in certain oncoplastic operations but this is also equally true for the standard practice of surgical clip placement in oncoplastic surgery cases. Justifying the newer intervention of Biozorb at a higher price thus is not supported given the lack of any evidence showing Biozorb to be superior clinically to surgical clips.

There are a few limitations to consider to our study. First, the reliance on literature review and retrospective data make it difficult to understand possible confounding variables. The reliance of this study on other published studies could result in confirmation bias, as our analysis depended on unbiased clinical results of other studies. To overcome this, we performed a systematic review utilizing formalized guidelines to identify all potential studies. Second, the variability between surgical technique and outcomes could not be fully accounted for given the retrospective nature of the study. A future prospective study comparing Biozorb vs. traditional surgical clip placement is needed to address these limitations; nonetheless, the burden of proof in showing clinical superiority always lies on the newer intervention (Biozorb). Lastly, a cost-utility analysis is dependent on the reliability of available literature, which was difficult to account for. Per the results of our systematic review, only 5 articles to date have evaluated the use of either Biozorb or surgical clips in marking the tumor bed for radiation planning purposes.

Even with these limitations in place, there are important implications of this study on our healthcare's economy and clinical practice. In recent years, healthcare spending has garnered lots of attention from researchers, clinicians, policy-makers, and the public. A report in 2014 revealed that healthcare spending is nearly averaging about 17% of the GDP (Lornezoni et al., 2014; Campbell, 2009). A healthy portion of healthcare spending goes towards oncological treatments and management. A study in 2009 estimated the life-time per patient costs of breast cancer to range anywhere from \$20,000 to \$100,000 (Fu, 2012). Another study demonstrated the large up-front costs to the healthcare system (Gallet, 2017). Given these large costs and the high prevalence of breast cancer in the United States, it is imperative to understand ways to reduce cost without sacrificing clinical quality or health outcomes. From a health care cost perspective, adding potentially \$1200 per oncoplastic operation, which would occur with widespread Biozorb adoption, would add a non-justifiable cost to our already cost strained health system. Major breast cancer centers have reported performing oncoplastic surgery on approximately 18% of all their breast cancer patients (Carter et al., 2016). Assuming there are approximately 230,000 new breast cancers diagnosed a year with 18% of these cancers receiving oncoplastic surgery, widespread adoption of the Biozorb (assuming it will be used in every oncoplastic surgery case) would add approximately \$50 million dollars a year (over the use of surgical clips) to the health care system (Siegel et al., 2014). Again, no reasonable clinical data shows substantial clinical superiority of Biozorb over surgical clips to justify this annual high additional cost.

The importance in this article's results cannot be understated. Surgeons need to actively monitor value in the surgical decisions they make, by prioritizing clinical benefit while respecting potentially added cost whenever a newer technique or device is brought up as an alternative to an existing standard technique or device. This study's goal is not to show Biozorb as a clinically superior or inferior technique in marking a tumor bed when

comparing it to surgical clips; it is to report, using PRISMA literature review guidelines, that limited data exists on this topic. However, the burden to prove Biozorb's clinical superiority lies with the company that manufactures the device, in ways such as appropriately funded comparative studies, etc. Most importantly, by using the results demonstrated here, the surgeon can be empowered to make an educated, value-based surgical decision, noting that no evidence present justifies value in the wide spread use of Biozorb over surgical clips in the marking of the tumor bed when performing oncoplastic surgery. Such ownership in value based surgical decision making by the surgeon maintains and justifies future autonomy and minimizes further regulation (by the hospital or government) on surgical choices.

5. Conclusion

In summary, literature and data on the clinical benefits of various tumor bed marking modalities in oncoplastic surgery is very limited. In oncoplastic surgery, the use of clips to mark the tumor bed is more cost-effective than the use of the Biozorb device which does not provide value given its relative high cost and lack of clinical advantage scientifically shown over the use of surgical clips. The burden of proof in value lies on the Biozorb device to show value before its widespread adoption in oncoplastic surgery since it is the newer and costlier intervention.

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