Balloon brachytherapy for breast cancer prove that it works? Or, prove that it doesn't?

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Abstract Balloon breast brachytherapy is a catheter-based technique to deliver high local concentration of radiation following breast-sparing surgery. Although this technique is logically appealing—providing more directed radiation to sites at high risk of local failure—there remains little empirical support that this intervention is non-inferior to external beam radiotherapy, a well-established standard. Additionally, observational studies suggest that balloon brachytherapy is associated with high rates of local complications, and higher rates of subsequent mastectomy, a marker of local failure. Here, I explore regulatory and clinical considerations that lead to the widespread adoption of breast brachytherapy. I argue that the therapy spread before its efficacy was confirmed. Breast brachytherapy illustrates ongoing complexities in the approval of novel devices.

Keywords Balloon brachytherapy · Mammosite · Evidence-based medicine

Introduction

Recently, one observational study identified frequent and concerning harms (Presley et al. 2012) and another found lack of efficacy (Smith et al. 2012) for a widespread, but unproven medical practice: the use of a balloon breast brachytherapy (BB) catheter to deliver local radiation after breast-conserving surgery (BCS). Using a large Medicare

data set, the first group found that BB yielded a 16.9 % higher rate of skin and wound complications (95 % CI 10.0–23.9; $P < 0.001$) and a 25 % increase in all complications (34.3 vs. 27.3 %, $P < 0.001$) compared to the standard treatment of whole breast irradiation (WBI) (Presley et al. 2012). Another group found that the 5-year incidence of subsequent mastectomy—a measure of treatment failure—was higher with BB (3.95 vs. 2.18 %, $P < 0.001$) than WBI and persisted despite multivariate adjustment (hazard ratio = 2.19, $P < 0.001$) (Smith et al. 2012). Together, these studies call into question 15 % of breast-conserving treatment (BCT) (Smith et al. 2011) and nearly 2 billion dollars in annual sales. (<http://www.prweb.com/releases/brachytherapy/endovascular/prweb2483664.htm>).

Proponents of breast brachytherapy have faulted both these studies (Cuttino et al. 2013), pointing to the methodological weaknesses inherent in observational study design (Ioannidis 2012) and prompting a fascinating dialog. The exchange highlights many of the challenges with our current paradigm of evaluating and adopting novel medical practices. Understanding BB can clarify patterns of use of medical practices.

The history of breast-conserving therapy

The evidence base for breast-conserving therapy originates in the National Surgical Adjuvant Breast and Bowel Project's (NSABP) seminal B-06 trial. That study (Fisher et al. 2002) found that lumpectomy with radiation yielded equal long-term survival as mastectomy and better local control than lumpectomy alone. In 1991, a consensus panel, relying on these results and others, declared that breast-conserving therapy should be the preferred choice for most patients with local breast cancer (NIH Consensus

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Development Conference Statement on the Treatment of Early-Stage Breast Cancer 1991).

Whole breast irradiation was not without consequences, however. Meta-analyses of radiation therapy after BCS noted an excess incidence of second malignancies (absolute excess of 1 %) (Galper et al. 2002). And, a pooled analysis of radiation after BCS or mastectomy has found an increase incidence of contralateral breast cancer, soft tissue sarcoma, and esophageal cancer. Regarding mortality, this analysis suggested an increase in non-breast cancer deaths (annual odds ratio 1.12, $p = 0.001$), mostly due to elevated rates of heart disease (odds ratio 1.27, SE 0.07, $2p = 0.0001$) and lung cancer (odds ratio 1.78, SE 0.22, $2p = 0.0004$), but also increased deaths from pulmonary embolism (1.94, SE = 0.41, $p = 0.02$) (Clarke et al. 2005).

In the mid-1990s, in an effort to deliver more targeted radiation, novel delivery mechanisms were investigated. Initial attempts used interstitial BB, or the implantation of radioactive beads. However, by the 2000s, intracavitary (balloon) catheter techniques were pioneered. In this technique, a balloon is expanded in the empty lumpectomy cavity, expanding the tissue deficit, and the catheter core is filled with radioactive seeds. The device was thought to deliver higher doses of radiation to the sites of greatest vulnerability, and theoretically improve outcomes, or at a minimum improve upon the harms of WBI (Aristei et al. 2009; Njeh et al. 2010). By 2006, balloon or catheter techniques comprised 89 % of brachytherapy in the United States (Smith et al. 2011).

Early randomized studies

Early randomized controlled trials comparing BB to conventional WBI were attempted, but these were of small sample size (only 88 patients received brachytherapy) and relatively short follow-up (median 66 months), and thus, unable to exclude clinically meaningful differences in rates of local recurrence or overall survival (Polgar et al. 2007). These numbers appear inadequate when contrasted to the approximately 60,000–100,000 patient-years of follow-up for WBI (Smith et al. 2011; Clarke et al. 2005). Larger randomized studies comparing the two modalities have begun, but results have not been reported. One study, the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast working group phase III multicenter accelerated partial breast irradiation trial, aims to randomize 1,170 patients to BB or WBI, and results are expected in 2014 (Cuttino et al. 2013; Belkacemi et al. 2013). It is worth noting, however, that the GEC-ESTRO study is examining the use of interstitial

BB only, and not balloon BB (Polgar et al. 2007). Other trials exist, such as the NSABP's B-39/RTOG 0413 trial, but these consider BB alongside three-dimensional (3D) conformal external beam radiation therapy techniques (NSABP PROTOCOL B-39 RTOG PROTOCOL). The choice of treatment (BB vs. 3D external beam) is based upon investigator discretion, and thus, due to selection choices, this trial may still leave unanswered questions regarding BB. Finally, it is worth noting that although I am confining my analysis to balloon breast brachytherapy, other focal breast radiotherapy techniques lack robust data. For instance, intraoperative breast radiotherapy was found to have similar rates of local failure in randomized trials; however, non-inferiority margins are wide and cannot exclude clinically meaningful differences (Vaidya et al. 2010; Veronesi et al. 2013).

Approval of brachytherapy devices

The US Food and Drug Administration approved the single-entry, single-lumen MammoSite® in May 2002. (NSABP PROTOCOL B-39 RTOG PROTOCOL) MammoSite approval was based on a single-arm study of 43 patients who received brachytherapy (Keisch et al. 2003) and followed to 28 days for side effects. Four (9.3 %) patients had either abscess or seroma formation, and 57 % had skin erythema (Keisch et al. 2003). The device was approved through the 510(k) approval process (Access Drug Approval Data), which grants approval based solely on equivalence to an existing device, and neither safety or efficacy data. The 510(k) mechanism has been criticized (Prasad et al. 2013a; Ardaugh et al. 2013), and the Institute of Medicine recommends it be discontinued (Institute of Medicine 2011).

Several other devices have been approved in the years since and increasingly incorporated into practice. These include the MammoSite ML (NSABP PROTOCOL B-39 RTOG PROTOCOL), Contura MLB (Brown et al. 2011), and strut-adjusted volume implant (Yashar et al. 2011). All three devices were cleared through the 510(k) mechanism.

Medicare reimbursement

Medicare agreed to cover BB in 2004 (Smith et al. 2011). Initially, reimbursement was set at 20,000 dollars, double that of WBI (The Evidence Gap Quickly Vetted, Treatment Is Offered to Patients). This was motivated by Medicare's longtime policy of providing more generous reimbursement upfront to compensate providers for initial outlays to purchase and support new technologies (The Evidence Gap

Quickly Vetted, Treatment Is Offered to Patients). Nevertheless, the imbalance continued for several years [by 2008, Medicare reimbursed 15,000 for BB, and 12,000 for WBI (The Evidence Gap Quickly Vetted, Treatment Is Offered to Patients)], which resulted in a surge in the usage of the device (Smith et al. 2011). By 2009, 15.8 % of Medicare beneficiaries underwent BB instead of WBI (Presley et al. 2012).

Data presented at the 2013 *American Society for Clinical Oncology* conference brought the use of BB under further scrutiny. One group analyzed data from over 35,000 Medicare beneficiaries treated with BCT at 2,255 nonprofit hospitals and 420 for-profit hospitals. They found that for-profit centers were 33 % more likely to use BB (20.2 % of breast cancer cases compared with 15.2 % at nonprofit hospitals, OR 1.5, $P < 0.001$) (Sen et al. 2013).

Brachytherapy today

As of today, several facts are true regarding BB. These intracavitary catheters now comprise more than 15 % of all breast-conserving therapy and cost society upwards of a billion dollars annually. They trace their approval through a regulatory mechanism, which requires neither efficacy nor safety data. Their current evidence base lacks a single adequate randomized trial showing, at a minimum, clinical equivalence to an existing and well-tested standard, and several observational studies show harms of the therapy, including evidence of higher treatment failure. From a neutral vantage, balloon BB highlights the ongoing challenges to our rational adoption of new technology, and the role perverse financial incentives may play.

BB proponents

Yet, recent observational studies demonstrating harm and lack of efficacy have provoked a dramatic response from BB proponents. Cuttino and colleagues fault both the recent studies and accept neither conclusion, noting that observational studies are “especially prone to methodologic and statistical biases that can render their results unreliable (Cuttino et al. 2013)”. They argue that since ongoing randomized trials are nearing accrual goals, “why, then, are retrospective observational studies that are based on billing claims necessary? What do these studies contribute? (Cuttino et al. 2013)”.

While there is some truth in these claims, at the same time, the authors miss the nuances of evidence-based medicine. First, it is true that observational studies often report point estimates that differ from randomized trials. (Ioannidis et al. 2001) Observational studies have

famously led to erroneous conclusions that subsequent randomized trials corrected (Ioannidis 2005; Prasad et al. 2012). However, while the limits of observational studies have been demonstrated for those that show the *benefits* of an intervention, they are not as well supported for those that identify *harms* (Papanikolaou et al. 2006). Empirical evidence suggests that observational studies do correlate with randomized trials regarding harms, and, if anything, fail to capture the full extent of harm (Papanikolaou et al. 2006).

The authors second point—“what does this add?”—is a philosophical question regarding research. Many contend that observational studies are hypothesis generating, but in this case, the hypotheses are all well known. Besides bringing the issue to discussion, strictly speaking, BB proponents are correct. The observational studies do not add much. Skeptics of BB’s effectiveness would not be convinced if the results found it non-inferior or superior to WBI and would continue to await the ongoing trials. What is equally true is that simply because the current findings are in line with the skeptics should not mean skepticism is any more justified.

Proving nonexistence

The central error made by proponents of BB is that the burden of proof to show whether or not a therapy works cannot rest with skeptics (Prasad and Cifu 2012). While the current observational studies are limited, proponents have not shown that BB is superior or even non-inferior (excluding a clinically meaningful difference) to WBI. Proving that a therapy does not work in any situation is un-falsifiable. Critics may contend that it would have worked had it been administered differently or deployed in the right patient population (Prasad et al. 2012). Showing a therapy works in a randomized trial is akin to showing how it can be operationalized. Under what circumstances can it benefit patients? In the absence of such studies, as with infinite theoretical interventions, we cannot embrace their use.

When it comes to BB, an alternative standard would be to demand prospective clinical trials either showing clinical superiority, or non-inferiority with reduced costs or improved side effects prior to the widespread use. One editorialist notes, regarding the on-going NSABP study, that had even a fraction of patients who have received BB in the community, “been treated on the trial instead of off protocol, the study would have closed... and we would already have the results. (Malin 2012)”.

When widespread medical practices are tested in well-done studies nearly half are found to be in error (Prasad et al. 2011, 2013b). Often these practices were adopted

based on minimal clinical evidence or pathophysiologic rationale alone, (Prasad et al. 2011) as in the case of BB. Thus, simply identifying medical practices that lack good evidence should warrant skepticism. If observational studies suggest that untested practices are inferior, our skepticism should remain, just as it should if these analyses are favorable. Many of the incentives in medicine are aligned to promote new therapies, but this is not synonymous with promoting health (Prasad et al. 2012). Our medical system cannot be one where proponents introduce practices based on preclinical data and await research to disprove them.

Breast-conserving treatment is a curative strategy, and as a general rule, oncologists are reluctant to deviate from a known cure to one of uncertain benefit. BB suggests that, with the right incentives, even this sacred guiding principle is negotiable. With breast brachytherapy, we have broken all the rules, and now, ten years after its approval, we must begin to fix them.

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