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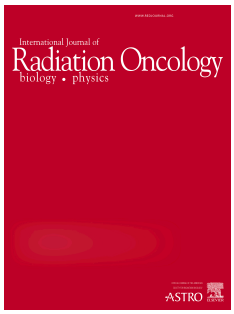

Systematic Review of Intensity-Modulated Brachytherapy (IMBT): Static and Dynamic Techniques

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Systematic Review of Intensity-Modulated Brachytherapy (IMBT): Static and Dynamic Techniques

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Running title: Intensity-Modulated Brachytherapy Review

Conflicts of Interest

Dr. Ryan T. Flynn has ownership interest in pxAlpha, LLC, which is developing a rotating shield brachytherapy delivery method. The current study presents analysis which includes prior studies by some of its own co-authors. All analyses - whether written, graphical, or statistical - were performed by authors not involved in the studies being analyzed. No authors in the current paper participated in the categorization, characterization, or editorial comments on their own past publications.

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Systematic Review of Intensity-Modulated Brachytherapy (IMBT): Static and Dynamic Techniques

Running title: Intensity-Modulated Brachytherapy Review

Summary

High-Z shielding of brachytherapy sources has long been used to increase the therapeutic index by improving target dose conformity. Recent novel applicators and sources increase the complexity and control that providers may have in delivering treatments with benefits in terms of sparing critical structures and dose escalation - typically at the price of longer delivery times. We evaluate the various levels of readiness for clinical implementation.

Abstract

Purpose: To systematically review scientific literature on the use of Intensity-Modulated Brachytherapy (IMBT) including static and dynamic shielding approaches to enhance therapeutic ratio. Studies were evaluated in terms of technique, disease site, dosimetry, applicators, dosimetric calculations, and planning algorithms. Comparisons to standard of care brachytherapy (BT) techniques and/or alternate IMBT methods were performed in terms of dose to target volumes, organs at risk (OARs), and treatment planning/delivery times.

Methods and Materials: Inclusion criteria were any peer-reviewed journal articles on IMBT published from 01/01/80 – 01/01/19 on PubMed, Google Scholar, Cochrane Library, and EBSCO databases. Two independent investigators reviewed each article for inclusion/exclusion criteria and scope. Data collected on each study included technique, source/shield material, disease site, *n* of study, dose to target/OARs, and planning/delivery times. This review adhered to the Preferred Reporting Items for Systemic reviews and Meta Analyses (PRISMA).

Results: Database query yielded 1,734 results which were reduced to 436 after exclusion criteria, and 78 peer-reviewed journal articles after evaluation of scope. Studies per disease site were 31, 16, 10, 7, 6, and 8 for cervical, rectal, oculocutaneous, breast, prostate, and other/multiple/no specific disease site respectively. Eighteen studies demonstrated significant decrease in dose to OARs (5.1-68.2%), 11 improved treatment planning/delivery times (7.6-99.7%), and 6 increased target coverage (18.6-71.6%) relative to standard of care or alternate IMBT technique. IMBT consistently decreased dose to OAR compared to standard of care at the cost of increased planning/delivery times. Innovations in dose calculation/planning algorithms and applicators were capable of ameliorating prolonged treatment intervals.

Conclusions: IMBT techniques improved therapeutic ratio by reducing OAR doses and/or dose escalation. Static shielding techniques are clinically available due to the advent of commercially available heterogeneity-corrected dose calculation algorithms while dynamic shielding techniques are still pre-clinical.

Key Words: Intensity Modulated Brachytherapy (IMBT); Treatment delivery devices/aids; Intensity-Modulated Radiotherapy; High-dose-rate brachytherapy; Low-dose-rate Brachytherapy

I. INTRODUCTION

Despite advances in external beam radiation therapy (EBRT) modalities such as volumetric-modulated arc therapy, image-guided radiation therapy, and stereotactic-body radiation therapy – brachytherapy (BT) remains an essential treatment option for many cancer patients. It can offer patients shorter treatment durations, decreased dose to healthy tissues, and may be much more cost effective than EBRT with comparable, or in select cases superior, patient outcomes [1,2]. In order to optimize patient outcomes with BT and increase the number of patients for whom BT is a viable treatment option, methods which increase the therapeutic index is critical. A brachytherapy source will naturally produce a symmetric isotropic field, but this may not produce the most conformal plan possible, especially for irregularly shaped tumors or those in close proximity to an Organ-At-Risk (OAR). The use of high-Z materials as a 'shield' for a specific OAR has a long history. More recently techniques using a shielded applicator or source to modulate the intensity of radiation dose during BT delivery, or 'Intensity-Modulated Brachytherapy' (IMBT), have been investigated. In this review, we categorize the various methods of IMBT into two broad categories of 'Static-' vs 'Dynamic-shielding' based on whether or not the orientation of the shield changes relative to the source during treatment.

'Static' IMBT approaches include those in which the shield does not move relative to the source or surrounding tissues during BT delivery and includes techniques such as shielded-applicators (e.g. shielded cylinder [3-11], shielded tandem and ovoids [12-20], Strut-Adjusted Volume Implant (SAVI) [21], Intracavitary Mold Applicator (ICMA) [22-26], Direction-Modulated Brachytherapy (DirMBT) [21,25,27-34], and Cup or D-shaped applicators [35-52]), and shielded

sources (Directional Low-Dose-Rate (LDR) implants [53-64]) (Figure 1). 'Dynamic' IMBT encompasses techniques in which the shield changes orientation relative to the source/tissue during treatment. This includes Rotating-Shield Brachytherapy (RSBT) [65-80], and Dynamic Modulated Brachytherapy (DMBT) [24,25].

In this study, we conduct a systematic review of IMBT literature and then analyze the investigations by disease site, technique, planning algorithm, and study type. Where possible we aim to compare and contrast IMBT techniques to each other and to standard of care conventional BT in terms of therapeutic ratio, delivery time, and practical application.

II. METHOD AND MATERIALS

A. *Literature Search*

Inclusion criteria for literature searches included any peer-reviewed journal articles published from 01/01/1980-01/01/2019 of PubMed, Google Scholar, Cochrane Library, University of XXXXX Elton B. Stephens Co. (EBSCO) databases, and University of XXXX Library Catalogs. Searched terms included: “Brachytherapy Methods”, “3D-Conformal Brachytherapy with Shielding”, “High Dose Rate Brachytherapy Shielding”, “HDR Brachytherapy Shielding”, “Intensity Modulated Brachytherapy”, “IMBT”, “Static IMBT”, “Dynamic IMBT”, “Dynamic-Modulated Brachytherapy”, “Direction-Modulated Brachytherapy”, “DMBT”, “Rotating-Shield Brachytherapy”, “Cup-shaped”, “D-shaped”, “Electronic Brachytherapy”, and “RSBT”. An exhaustive list of Medical Subject Headings (MeSH) terms and specific advanced search engine parameters can be found in supplemental material.

Published proceedings from American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO) and the European Society of Radiotherapy and Therapeutic Oncology (ESTRO), American Brachytherapy Society (ABS), American Association of Physicists in Medicine (AAPM) annual meetings were also reviewed for relevant abstracts. If a subsequent manuscript related to that abstract was published it was also included. The Physician Data Query (PDQ) and *Clinicaltrials.gov* were searched for relevant ongoing trials. References from included sources were searched manually for any other relevant studies. Cited literature from any collected manuscript which also met inclusion criteria was also included. The last search was conducted on January 1st, 2019. Articles accepted for publication in press

were also included. Published theses and dissertations were included. Exclusion criteria included studies without an English version or translation available, non-peer reviewed literature, and studies unrelated to IMBT.

Two independent investigators (XX & XX) reviewed titles, abstracts, and articles to determine if each study met inclusion criteria as well as category of technique and scope of study. Any discrepancy was settled by a third independent investigator (XX or XX). Data collected on each study included title, author(s), year of publication, IMBT technique/method, source/shield material, disease site, comparison (to conventional BT vs other IMBT method), dose calculation and planning algorithm, target coverage, dose to OARs, *n* of study, and delivery times.

This systematic review adhered to the Preferred Reporting Items for Systemic reviews and Meta Analyses (PRISMA) (Figure 2) with flowchart of database searches available in supplemental materials. Review search protocol can be accessed at (http://XXXXXXXX), or review registration # XXXXXX at PROSPERO website. Full electronic advanced search strategy for database searches available in supplemental material.

B. *Review and Synthesis*

Studies included in the final qualitative synthesis were analyzed by disease site and technique. If reported in the original manuscript, doses to target and OARs as well as planning and delivery times were included. Studies with comparisons between IMBT and conventional BT and/or alternate IMBT techniques were summarized in absolute or relative terms. Studies were too heterogeneous to perform meaningful meta-analysis of aggregate data.

III. RESULTS

A. *Literature Search*

Database queries yielded 1,734 cumulative results. Screening of abstracts excluded 1,189 studies on the grounds of date restrictions, language, not a peer-reviewed journal article, or full text of study unavailable. Subsequently, 109 studies were excluded as duplicates or were determined to be out of scope upon review of abstract. An additional 358 were determined to be out of scope after review of the full text. This resulted in the inclusion of 78 peer reviewed articles to be included in the final qualitative synthesis (Figure 2). Table 1 shows distribution summary by disease site and technique. An exhaustive catalogue of all IMBT studies which met criteria is listed on Table 2 with full citations in 'References' section. Two studies for conceptual IMBT were reported with no specific applicator design [81,82]. Twenty-five studies were on clinically implemented IMBT techniques [6,7,23,26,35,36,38-43,47-49,53,56,58,63,83-88], thirteen included a prototype of the applicator [3,4,18,19,27,28,31-34,66,73,78], with the majority of other studies using simulated IMBT plans on real patients' simulation scans or dosimetric evaluations.

B. *IMBT per Technique*

Per our categorization, the major separation was into static versus dynamic IMBT techniques. 'Static' techniques included any shielded technique in which the shield did not move relative to the source/regions of interest during treatment. The shield could be

197 associated with the applicator or the source directly (sub-categories 'static-shielded applicators'
198 [3-44,46-49] and 'static-shielded sources' [53-64] respectively) but a given approach was not
199 included if a static shield was solely associated with an OAR for its sparing, and not with the
200 source/applicator (*e.g.* mandibular shields in head and neck brachytherapy). Techniques were
201 considered 'dynamic' if the shield was translated or rotated during treatment relative to the
202 source/regions of interest as part of the treatment plan. The sub-categories of dynamic IMBT
203 being 'dynamic-shielded applicator' [24,25,67,69,74-80] or 'dynamic-shielded source'
204 [65,66,68,70-73], again based on whether the shield was associated with the applicator or the
205 source. It is helpful to refer to Figure 1 throughout the following descriptions to visualize
206 unfamiliar applicators and techniques.

207 In addition to these techniques, in some cases multiple planning algorithms were tested
208 to optimize planning time and delivery time – the results of which are mentioned in the
209 'Technique' section as these aspects are more related to the technique and planning algorithm
210 than a particular disease site. Doses to target and OARs are discussed under the 'Disease site'
211 section as those are more related to specific pathologies and their local anatomy.

212 Static-shielded IMBT

213 *Static-shielded sources*

214 IMBT approaches of static-shielded sources have been introduced to spare OARs using
215 low-energy photon-emitting sources, commonly I-125 or Pd-103 as LDR implants for breast
216 cancer BT [60,89], prostate cancer BT [90], ocular melanoma (Figure 1B) [53,56,57,59,61,64] or
217 intraoperative BT for pancreatic, abdominopelvic, and colorectal cancer [54,55,58,62,63]. Lin et
218 al. introduced directional D-shaped I-125 sources with 0.2 mm-thick gold shield for interstitial

LDR-BT in order to achieve an angular uniform dose over a 180 degree sector around the axis of the source in the transverse plane [60].They reported dosimetric validation results for breast cancer when compared to Ir-192 based HDR-BT plans and the treatment planning technique for the directional, D-shaped LDR source (Figure 1C) was developed using an automated 3D greedy heuristic optimization algorithm and validated for prostate cancer [90]. Heredia et al. tested the use of Pd-103 source with 0.03 mm-thick osmium metal shield for the directional D-shaped LDR source design [89]. Aima et al. developed a watch-battery shaped, polymer encapsulated Pd-103 source with gold shield (Figure 1A) called the CivaDot™ (CivaTech Oncology, Inc., Durham, NC) and a planar CivaDot array called CivaSheet™ which size has a width and length of 5 x 15 cm^2 with 8 mm spacing between the center of each CivaDot, yielding 108 dots in eighteen rows of six [54]. The sheet can be cut depending on the size of the treatment area. Each CivaDot is oriented such that the gold shields are all on the same side of the CivaSheet yielding a hot and cold side of the sheet. The static-shielded source approaches are mainly targeted to improve the therapeutic ratio for a given brachytherapy treatment by sparing OAR doses. No increase in treatment or delivery times were reported for these static-shielded sources.

Static-shielded applicators

The first static-shielded applicators were introduced by Neary and Blomfield in 1947 to reduce bladder and rectal doses for cervical cancer treatment [91]. Five years later, Fletcher et al. developed a shielded colpostats (ovoids) with a tandem applicator along the line of the Manchester technique which is the original design of widely used Fletcher-Suit-Delcos tandem-and-ovoids (T&O) applicator [14,16,92,93]. The Henschke applicator is another design with semispherical applicators featuring bladder and rectal shielding [17,20] (Figure 1E,F).

Static-shielded applicators also include cup or D shape applicators in which the applicator is pressed up against the surface of the skin as with Zeiss INTRABEAM® (Carl Zeiss Meditec AG, Jena, Germany) [50-52], Leipzig or Valencia applicators (Elekta Brachytherapy, Veenendaal, The Netherlands) [35,39,43,94], the breast as with Accuboost™ (Advanced Radiation Therapy, Inc., Billerica, MA) [37,41,42,44,47]), or colorectal tissue as with Papillion devices (Ariane, Alfreton, UK) [36,38,40,45,46,48,49,84-88,95,96]). Leipzig applicators have been studied and used clinically for non-melanoma skin cancer or Kaposi's sarcoma [43], are conically shaped with tungsten or tungsten alloy shields of 10-30 mm's in inner diameter, and utilize Ir-192 source in either parallel or perpendicular orientation to the treated surface (Figure 1J). Dosimetric studies have also characterized the use of Co-60 and Yb-169 HDR sources compared to Ir-192 for the Leipzig [94]. Valencia applicators are essentially the same but with the addition of a flattening filter [97-100], while Zeiss applicators (INTRABEAM®) employ electronic brachytherapy (eBT) sources [50-52]. Papillion devices are similar in concept but clinically used for colorectal cancers or occasionally conjunctival malignancies [83]. Papillion devices also have a conical opening but utilize eBT sources generating on average 50 kVp low-energy photons, and are introduced into the rectal cavity via proctoscope with stainless steel casing (Figure 1I). Devices such as Accuboost™ [101] are used in the setting of breast cancer to provide a boost to the post-operative bed by using an applicator placed on the skin surface in a 4-field box along an orthogonal axis of a compressed breast. These applicators can be either round or D-shaped, with 6mm thick Tungsten alloy (90% W, 6% Ni, and 4% Fe by weight) shields and a 4.5mm polycarbonate disk to house Ir-192 sources (Figure 1H) [102-105].

For rectal cancer a number of papers have discussed Intracavity Mold Applicators (ICMA) with a central shielding rod (tungsten, 8 mm diameter surrounded by 8 channels through which Ir-192 sources can be translated (Figure 1G) [22-26]. This allows for partial shielding for the tissue opposite of any given dwell position.

Grooved-shielding HDR applicators (Figure 1K,L,M), also known as Direction-Modulated Brachytherapy (DirMBT) applicators, for rectal cancer [25], breast cancer [21], and cervical cancer [27-33] have relatively recently been introduced with the advance of dose optimization and heterogeneity-corrected dose calculation techniques. In this technique a central high-atomic number (Z) tandem or cylinder has 'grooves' symmetrically placed around the periphery into which sources can be translated. The dose distribution is modulated by the direction of the groove in which the source is placed relative to the applicator (ergo the term DirMBT). This is similar to the ICMA technique but the channel through which source is translated in ICMA is not embedded in the shield as are the grooves in DirMBT (Figure 1). For rectal cancer applications, Webster et al proposed a tungsten cylinder 16 mm in diameter with 8-16 grooves of 1-3 mm in depth (Figure 1L) [25] . For breast cancer applications in a lumpectomy cavity a 1 cm diameter tungsten cylinder with 8 channels 1 mm in depth was proposed with a novel ellipsoid cap of 1 cm in length (Figure 1M) to compare to shielded SAVI techniques (Figure 1D) [21] The most well studied application of DirMBT is found in cervical cancer where a tungsten alloy tandem of 6 mm in diameter with 6 peripheral channels of 1.3 mm depth is employed with Ir-192, Co-60, or Yb-169 sources (Figure 1K) [27-34].

As expected, static shield IMBT methods did increase delivery times by 25-319% relative to conventional BT plans [21,25,28]. However, these increases still yielded clinically feasible

absolute delivery times of ~20 minutes. Studies investigating the use of optimization algorithms specifically for IMBT found that the use of efficient optimization algorithm could reduce the total planning time by a factor of ~ 60 (a 98.4% relative reduction, ~20 minutes vs 20 seconds absolute planning time) [23,26]. These studies involved shielded cylinders and multi-channel tandems in rectal and cervical cancer applications.

Dynamic-shielded IMBT

Dynamic-shielded sources

In 2003 Kim et al. described a theoretical model of a cylindrical Sr/Y-90 source in which either one half or three quarters of the cylinder was replaced by a stainless steel or tungsten shield which could then be rotated to deliver an anisotropic dose distribution [72] (diameter 0.68 mm, height 2.5 mm) (Figure 1N, Table 2). Adams et al. explored the use of interstitial needles for prostate cancer in which an eccentric source associated directly with a platinum shield (0.5-0.6 mm) and a low-attenuation aluminum window (75 μm) (Figure 1O), rotates within a nitinol needle (1.6 mm)[66]. The dosimetric parameters of this applicator were studied for a Gd-153 source [71], extensively for multisource (up to 20) angular drive mechanism and remote after loader for practical implementation (with loss of inner nitinol catheter and alterations of various dimensions) [68], and their follow up study utilized more patient-simulated plans and focused on urethral sparing and dose escalation [65].

Delivery time increases of 1283-1440% (154 vs 12 minutes and 216 vs 15 minutes respectively) were observed with dynamic shields associated directly with the source for use in interstitial prostate IMBT using Gd-153 compared to conventional HDR-BT using Ir-192 [65,66]. No planning times were reported for dynamic source IMBT techniques.

306 *Dynamic-shielded applicators*

307 Webster et al 2012 presented a dynamic-shielded IMBT applicator for rectal cancer
308 treatment [25] labelled as "Dynamic Modulated Brachytherapy" (DMBT). A rotating tungsten
309 cylinder (45 mm height, 19 mm diameter) with a 45-degree wedge-shaped opening housed a Ir-
310 192 source at the wedge apex, 3 mm eccentric from the radial center (Figure 1P). This provides
311 a high intensity emission window. This was later compared to both shielded ICMA applicators
312 and DirMBT applicators [21].

313 Ebert et al. in 2002 first introduced the concept of "… *radially asymmetric internally*
314 *applied radiation sources* …" and that it would require shielding and rotation of the high-
315 intensity non-shielded window [81]. In 2013 Yang et al. described "Rotating Shield
316 Brachytherapy" (RSBT) using an eBT source (Patented by Xoft Inc^{TM} [106]) with a single 0.5 mm
317 tungsten shield (45 or 180-degree unshielded window) which could rotate around a central axis
318 (Figure 1Q). This maintains a high intensity emission window which does not change in
319 dimensions. This differs from the above described DMBT technique in that the source remains
320 on the central axis and is not directly in contact with the shield in a wedge-apex (Figure 1P). A
321 subsequent study presented a more complex model of RSBT, in which two tungsten shields
322 (thickness 1 mm) rotated independently around a 50 kVp eBT source. The inner and outer
323 shields could translate past one another and therefore could dynamically alter the dimensions
324 of the unshielded high intensity emission window in addition to controlling its direction (Figure
325 1O) [76]. It was therefore called "Dynamic RSBT" (D-RSBT) while the previous technique using a
326 single shield was called "Single-shield RSBT" (S-RSBT) (Figure 1Q,R). Paddle based RSBT (P-RSBT)
327 was reported in 2015 by Liu et al in which 'paddles' of 0.5 mm tungsten could be drawn into or

pulled out of the field to shield an eBT source. These shielding paddles together constituted independent segments encircling the source which could be advanced or withdrawn to shape dimensions of the emission window(s) as well as rotated around the central axis (Figure 1S) [74]. Dadkhah et al. in 2015 presented a Multihelix RSBT applicator (H-RSBT) for cervical cancer [68]. In this model the 9.4 mm diameter tandem contains six internal helical keyways into which protruding keys on a partial 0.5 mm tungsten shield surrounding an eBT source are inserted. As the source is advanced, high-Z shield rotates as it is translated through the helical keyways (Figure 1T). This approach addresses the mechanical difficulties associated with implementing the previously mentioned RSBT modalities.

Dynamic shielded applicator IMBT methods variably added to total delivery times due to its shielding by 20-770% compared to conventional HDR-BT [25,28,68,75,80,107].

No Specific Applicator Design

In 2010 Shi et al. presented heterogeneity-corrected dose calculation algorithms and inverse treatment planning for a simulated IMBT applicator that was based upon an accelerated partial breast irradiation (APBI) balloon applicator (Xoft Axxent, iCad, Inc., CA, USA) and whose emission window was capable of modulation in both the polar and the azimuthal angle [82]. No details of APBI IMBT applicator design were presented but planning study results for 10 APBI HDR-BT patients were reported. The IMBT optimization time for a simulated APBI IMBT applicator was reported was capped at 120 minutes compared to ~5-minute optimization time for single dwell position APBI HDR electronic BT plans [82]. Delivery times for IMBT plans were ~35-38 minutes compared to 5-8 minutes for conventional/isotropic APBI HDR electronic BT plans for breast cancer.

IMBT Optimization Algorithms

Regarding most static IMBT applicators, model-based dose calculation algorithms (MBDCAs) that are now available for most major treatment planning systems can be used to calculate heterogeneity-corrected dose calculations [108]. Commercial MBDCAs usually perform the volume optimization using AAPM Task Group 43 formula [109], while a recently updated version of MBDCAs (Acuros, BrachyVision v15.1, Varian Medical Solution, Inc. Palo Alto) enables heterogeneity-corrected dose calculations during inverse-optimization. For the use of dynamic IMBT applicators, MBDCA-based inverse optimizations are commercially available but remain in pre-clinical stages of development. Some static IMBT applicators such as DirMBT also require MBDCA-based inverse optimization [24,28-31,107]. Pioneering investigations have been performed to improve IMBT plan quality, delivery time, and treatment plan optimization time by improving its inverse optimization algorithm [67,75,77] or emission angle selection algorithm [77]. A rapid emission angle selection (REAS) algorithm was proposed to efficiently determine azimuthal radiation beam emission angle for RSBT approaches, presenting 19.5 – 21% improvements in HR-CTV coverage (D90) when compared to conventional approaches of exhaustive dose-volume optimization or exhaustive surface optimization. Liu et al. 2014 proposed to the use of the asymmetric dose-volume optimization with smoothness control method (ADOS), and presented 3.5 – 8% and 6.5 – 16% improvements in plan quality measured by HR-CTV D_{90} with same OAR sparing when compared to the dose-surface optimization and inverse-planning with simulated annealing (IPSA), respectively [75]. The proximal graph solver (POGS) that is a convex optimization solver using the alternating direction method of multipliers was reported to be 18 times faster than commercially available solver (IMB ILOG

CPLEX). The ADOS algorithm was tested using both S-RSBT and D-RSBT, while POGS algorithm was validated using H-RSBT [75]. All optimization efficiency studies have been performed using CPU-based dose calculation [67,75,77]. A GPU-based Monte Carlo (MC) dose calculation for HDR-BT was tested and completed the optimization in less than 48 seconds with 0.15% statistical dose calculation uncertainty [79].

Electronic brachytherapy (eBT) Sources

Another aspect that has been studied in terms of IMBT technique is - not just the type of radioactive isotope source material – but an entirely novel category of x-ray production called electronic brachytherapy (eBT) where a miniature x-ray tube acts as the source [110,111]. The functional differences compared to radioactive isotopes include the ability to control when radiation is being produced, and theoretically the ability to modulate the energy and fluence of the photons. This has been studied in theoretical settings and in the context of RSBT [67,69,74-77,80].

C. *IMBT per Disease Site (Target and OAR Dosimetry)*

Below is listed the applications of IMBT with respect to disease site with relevant target and OAR dosimetric parameters in relation to that particular malignancy.

Breast Cancer

Currently, interstitial and intracavitary BT in breast cancer is used in the context of Accelerated Partial Breast Irradiation (APBI) after lumpectomy for a highly select group of patients as an alternative to whole breast irradiation (WBI). Despite randomized trials demonstrating equivalent local control [112,113], and less time investment for the patient,

and less cost [114], APBI brachytherapy is not as commonly employed as WBI. Reasons include the technical skill and training required on the part of the physician, but also patient exclusion due to anatomic location of the lumpectomy cavity leading to inability to meet dose constraints for OARs.

Increased rates of poor cosmesis (incidence 5-34%), fibrosis (45-54%), fat necrosis (15-35%), skin/subcutaneous toxicity (17-78%), pulmonary fibrosis, chest wall pain, and rib fracture have all been associated various dosimetric parameters in ABPI [41,115,116]. While clinical data has not yet established specific thresholds at which all of these toxicities reliably occur, society guidelines have suggested preferred goals in terms of Dose Homogeneity Index (DHI), V_{200}, skin D_{1cc}, Chest wall, and ipsilateral lung mean dose/$D_{0.1cc}$ [112,117]. Suboptimal cosmetic outcomes, Grade 1-2 late skin toxicity, increased late subcutaneous toxicity, and increased fat necrosis have all been associated with increased V_{200} and/or decreased DHI [118]. Increased incidence of chest wall pain has been associated with increased total dose to various volumes of the ribs [119].

The aim of IMBT studies in the breast has therefore been to decrease dose to OARs, reduce the volume of dosimetric hotspots, and to increase the conformality and dose homogeneity (DHI) of the treatment plan. When compared to HDR-BT plans, IMBT methods were favorable in terms of both reduced V_{200} 6.6-35.9% and increased Dose Homogeneity Index (DHI) 10.4-13.4% [21,60,82,120]. IMBT techniques also significantly decreased dose to OARs including skin (D_{max}/S_{30}/S_{50}/S_{80} 10.7-68.1%), lung (D_{max} 6.2-27.0%), and ribs/chest wall (D_{max} 8.7-159%)[21,60,82].

Breast IMBT may therefore reduce toxicities; but the shielding also has the potential to increase the number of patients eligible for APBI brachytherapy. In general, patients with tumor beds <5 mm from either skin surface or chest wall are currently not considered optimal candidates for conventional HDR-BT. The literature for conventional HDR-BT reports fairly low rates of chest wall pain and rib fractures (~21.3 and 1.8% respectively), likely as a result of these guidelines [112-115,117-119]. The reduced dose to these structures with IMBT suggests the possibility for reducing these margins, and therefor increasing the patient population for which APBI may be a viable option.

One clinically implemented IMBT method includes Accuboost™ (Advanced Radiation Therapy, Inc., Billerica, MA) [101] cup or D shape static IMBT applicators – used after lumpectomy and WBI to boost the tumor bed using mammography image guidance. Retrospective studies have demonstrated favorable incidence rates of Grade 1-2 acute skin toxicity (21-64%), Grade 4 toxicity (0%), Good/excellent cosmesis (97.8-100.0%) [41,42,47], and freedom from recurrence (97.6%) [47] at 3-12 months median follow up time.

Cervical Cancer

For conventional HDR-BT patients with D_{90} of <85 Gy_{EQD2} to HR-CTV have been shown to be at significant increased risk of local recurrence (overall incidence ~12.8%) compared to those with D_{90} >85 Gy_{EQD2} [121]. D_{2cc}'s greater than 80Gy for the bladder and 65Gy for rectum and sigmoid, have been associated with higher instances of ≥ Grade 2 acute and late toxicities with general incidences of 23.3% for bladder and 26.8% for rectosigmoid [122,123]. This typically translates to the dose to the HR-CTV being maximized until the OARs are at or near their dose

tolerances. Therefore, studies of IMBT in cervical cancer have attempted to either decrease D_{2cc} of the OARs, to increase D_{90} to the HR-CTV, or both (though as of yet not simultaneously).

In studies attempting to maximize HR-CTV D_{90}, IMBT techniques were capable of increasing D_{90} by 20.4-36.3% relative to conventional HDR plans [76,80,122,123]. In studies attempting to decrease D_{2cc} to OARs, IMBT techniques were capable of decreasing D_{2cc} to the rectum by 4.65 – 22.4%, sigmoid by 4.34–12.1% and bladder by 5.13–20.0% compared to conventional HDR brachytherapy [12,17,28-30,78]. This indicates that IMBT is capable of reaching treatment goals known to be associated with decreased rates of toxicity, as well as superior local control, compared to conventional HDR-BT.

Oculocutaneous

Static shielded sources have been utilized for ocular melanoma since at least 1966, when H. B. Stallard published a series of 99 patients treated with Co-60 plaques of 0.5 mm platinum [124]. Since its inception, only one study of unshielded brachytherapy for ocular melanoma has been published, and so there are generally no “conventional” BT techniques to compare with IMBT, and only incremental changes have been made to the plaque design (Figure 1B). Considerations for IMBT in ocular melanoma include the ability of the ophthalmologist to perform the plaque insertion, tumor thickness/diameter and location, and risks/benefits compared to enucleation or charged particle therapy. The largest potential benefit of IMBT is the potential for preservation of vision in the affected eye.

A retrospective review of 53 patients with choroidal melanoma treated with I-125 found that 32 patients had decreases in visual acuity, 12 patients remained stable and 9 patients experienced improvements. Survival was comparable to patients undergoing enucleation

(median follow up time of 1.3 years) [53]. Simulations and treatment planning studies have been performed for Pd-103, I-125, and Cs-131 sources [57,61]. A Monte Carlo simulation demonstrated that Cs-131 and I-125 sources were comparable using both Au and Au alloy for plaque material, with the alloy reducing dose 4% to the central axis, compared to 7% by the pure gold plaque [64]. One study found that the photon sources with energies ≤22 keV could provide better sparing of distal OARs so long as the prescription depth was <9 mm [59]. A recent retrospective study of 242 patients examined the use of a ruthenium Ru-106 and a 0.7 mm gold plaque (n=136) in comparison to proton beam therapy (n=106), both as adjuvant treatments after transscleral resection of uveal melanoma, with no significant difference in incidence of rubeosis iridis, neovascular glaucoma, or later enucleation [56]. One study using a Papillion device that is one of Cup- or D-shaped static IMBT applicator technique typically used for colorectal cancer for treatment of 14 patients with conjunctival melanoma, malignant fibrous histiocytoma, or other carcinoma were treated with 3-4 fractions of 10Gy using 50kV photons. After 33 months follow up 7% incidence of cataracts, moderate dry eyes, and local recurrence with no incidence of corneal ulcer [83].

Cutaneous malignancies have been treated with Leipzig applicators for contact brachytherapy since at least 1987 [125], and more recently with Valencia [97-100] and Zeiss [50-52] applicators. Since surgical resection has historically demonstrated lower rates of local failure - these techniques are typically employed in cases where the patient is older or cannot tolerate surgery, midface location, and in consideration of cosmetic and functional outcomes by patient preference [35]. Clinical studies of squamous and basal cell skin cancers have demonstrated favorable outcomes in terms of rates of complete regression of the lesion (98%),

good/excellent cosmetic outcomes (82-88%), local recurrence (2-4.4%), Grade 1 (57.3-71%) and 4 (2.2%) acute skin toxicities at 33-66 months follow up [35,39]. Similar results have been found with applications in Kaposi's sarcoma [43].

Prostate Cancer

HDR-BT for prostate cancer can be delivered with or without EBRT. Complications from BT for prostate cancer include urethral stricture, lower urinary tract symptoms, rectal toxicity, and erectile dysfunction. The incidences of these toxicities with HDR as a boost to EBRT are ~5.2-12.7%, 17-38%, 21-26% [68,126] and 20-50% respectively [127,128]. While new or worsening sexual dysfunction is very common following prostate BT, no consistent patterns have emerged demonstrating what structures might be spared to ameliorate this effect.

The incidence of urethral stricture has been associated with V_{150} and $D_{0.1cc}$ of the urethra/periapical urethra [126,129]. Lower urinary tract symptoms share a positive association with bladder D_{1cc} [130,131], with similar findings for with rectal toxicities and hotspots [127]. IMBT studies have therefore focused on decreasing dose to OARs, especially the urethra and periapical urethra, instead of increasing prescription dose, given the relatively good prognosis for patients receiving standard doses.

IMBT techniques decreased urethral $D_{0.1cc}$ by 31-44%, periapical urethral $D_{0.1cc}$ by 25-30%, Bladder D_{1cc} by 4-6%, Rectal D_{1cc} by 6-7% [66,68] and urethral $D_{10\%}$ by 26% [65] compared to conventional HDR-BT. Indicating that IMBT may be capable of decreasing sequelae, including urethra stricture, while maintaining coverage of the target volume for prostate brachytherapy. One study also demonstrated the ability to dose escalate with RSBT by increasing the PTV $EQD2_{90\%}$ by 42.5% relative to conventional HDR-BT [65].

Rectal Cancer

One of the most frequent toxicities associated with rectal cancer brachytherapy is diarrhea and radiation dermatitis with incidences of 50-60% [7]. One of the largest improvements in quality of life for a patient with rectal cancer can be whether or not they are able to undergo sphincter sparing resection, allowing preservation of rectal continence. This can be achieved using neoadjuvant chemoradiation and intracavitary brachytherapy boost to downsize the primary tumor such that a sphincter sparing resection may be possible with incidence of ~28-44% [7,132].

Brachytherapy for rectal cancer can be utilized neoadjuvantly, concurrently with chemotherapy and/or EBRT, in patients with close or positive margins after resection, for re-irradiation, local recurrences/salvage treatments, or palliatively. In such diverse settings, and when used in concert with as many as 3 other treatment modalities, it is difficult to determine which sequelae may be caused directly by endorectal brachytherapy. As such, there are little published data associating specific dosimetric parameters to toxicities attributed to endorectal HDR-BT directly. However, given known normal tissue tolerances, sequelae from EBRT to the pelvis, as well data from the context of prostate and cervical brachytherapy - metrics such as D_{mean}, D_{98}, D_{20}, D_{5cc}, and V_{90} of healthy rectal tissue are likely to share a direct association with acute diarrheal and skin toxicities in this setting.

IMBT techniques for rectal cancer have therefore aimed at decreasing dose to contralateral healthy rectal tissue for non-circumferential lesions. They have not yet explored maximizing dose to target volumes and have actually decreased target volume coverage in some cases. For contralateral healthy rectal tissue relative reductions in D_{mean} 24%, D_{5cc} 49.5-

59.6%, D_{20} 11.8-16.2%, V_{90} 22.4-33.6%, and ~40-60% reduction in D_{98} to all OARs evaluated relative to conventional HDR [23,25,26,107]. These findings bode well for the possibility of decreasing toxicity, especially in the context of salvage or re-irradiation, as well as possible organ sparing prior to resection. The decrease in target volume coverage was usually slight; V_{100} decreased by 1.3-3.0%, D_{90} reduced by 3.45-7.8% and CTV D_{mean} was reduced by 4.7-13.0% [23,26,107] relative to conventional BT. However, overall Dose Heterogeneity Indices (DHI) were decreased with IMBT methods by 27.1-38.3% relative to conventional BT [25,107].

Clinically, Cup- or D-shaped static IMBT applicators with Papillion devices have been the most widely used to provide boosts to early stage colorectal cancers for over 30 years [36,38,40,46,48,49,84-88,95,96]. Studies have demonstrated favorable incidence rates in terms of 3 year local recurrence (6-16.9%), clinical complete response (63.8-96%), organ preservation (62-96%), Grade III acute (constipation/diarrhea or incontinence, 6.7-9%) and late toxicity (bleeding, 9-28%), and good-excellent bowel function (85%) at 2.5-3 years median follow up [38,40,48,49].

Other, Multiple, or No Specific Disease Site

Studies of IMBT have also included other sites such as pancreas [63] multiple malignant sites (an ongoing clinical trial of any solid tumor of the abdomen or pelvis) [58], no specific disease sites [55,62], and non-malignant applications such as intravascular BT for coronary artery disease [72,81]. None of these studies performed systematic comparisons between conventional BT and IMBT plans in terms of target coverage and/or OAR sparing or inverse planning optimization and delivery times. However, some were clinically implemented, unlike the majority of previously mentioned studies [63].

Current Clinical Trials

Query of *clinicaltrials.gov* and PDQ yielded 2 ongoing trials of static-shield LDR methods for Pancreatic Cancer: NCT02843945 [133] and NCT03109041 [134]. Both are studies of CivaSheet™ static-shielded source IMBT for pancreatic cancer (Figure 1A). The latter is a Phase I study of pancreatic cancer patients undergoing Whipple procedure with implantation of the sheet occurring at the time of surgery. NCT02843945 is a Phase I/II trial of locally advanced/borderline resectable pancreatic cancer patients who underwent neoadjuvant chemoradiation and were selected to undergo Whipple/distal pancreatectomy with CivaSheet™ to be implanted at the time of surgery. In addition, the OPERA Phase III clinical trial (NCT02505750) randomizes patients with T2-T3b, N0-1, M0 rectal cancer to 45Gy of EBRT with concurrent capecitabine to either a 9 Gy (EBRT) or 90 Gy (Papillion brachytherapy) boost [135].

IV. DISCUSSION

The current state of IMBT literature is that it is well tested theoretically, with benefits repeatedly demonstrated in terms of decreased dose to OARs [21,23,25,26,28-30,60,65,66,68,78,82,120] and/or increased tumor coverage [65,76,80]. This often comes at the price of increased delivery times [21,25,28,65,66,68,75,80,82,107,120] and inverse planning optimization times [82], and has rarely been clinically implemented outside of the category of static-shielded applicators or directional LDR-sources.

In broad terms, the more a target volume diverges from a sphere/ellipsoid shape of an isotropic field, the more sensitive the regional OARs associated with clinical sequelae, and the more a particular target malignancy would benefit from dose escalation (but is otherwise constrained by those OARs limits) – the greater the potential benefit of IMBT over conventional BT. But these benefits can only be realized if the technique is clinically feasible in terms of implementation by physicians and medical physicists, planning and delivery times, and has mechanically viable applicators.

The most well described disease site is cervical cancer, with a variety of both static-shielded [8-10,12-20,27-34] and dynamic-shielded techniques [41,67,69,74-80]. These techniques demonstrated both the ability to dose escalate [76,80] and to reduce dose to OARs [12,17,21,23,25,26,28-30,60,65,66,68,78,82] in dosimetric measures specifically associated with

increased local control and decreased rates of toxicity to the bladder and bowel. In prostate cancer IMBT, mostly dynamic-shielded techniques have been studied [65,66,68,70,71]. They have been able to improve OAR sparing known to be associated with lower rates of toxicity – especially in relation to the urethra [65,66,68]. In breast cancer, IMBT techniques could possibly expand the number of patients that would be eligible for APBI by decreasing the number of patients whose anatomy would otherwise preclude them from that treatment option, though IMBT may not be able to offer sufficient advantage over SAVI to make its pursuit worthwhile in this context [21,60,82]. In rectal cancer, the treatment of non-circumferential tumors with endorectal IMBT did demonstrate the ability to decrease dose to contralateral healthy rectal tissue [23,25,26,107], but also had the concerning result of decreased target coverage in some circumstances [23,25,26,107].

In terms of technique, dynamic shielded-applicator RSBT (Figure 1Q-T) [65-71,74-80,136] and static shielded-applicator DirMBT approaches have been widely investigated (Figure 1K-M) [22,23,26-33]. Studies of both these techniques have included steps towards clinical implementation such as CT/MRI compatibility [27,33,34,78,137], optimal planning algorithms to decrease planning/delivery times [23,26,32,67,75,77], and optimal sources and shielding materials [4,29-32,71,138].

Commercially available IMBT techniques include static-shielded applicators [6,7,14,17,20,35-44,46-52,94] such as the Henschke and Fletcher-Suit-Delcos tandem-and-ovoids (T&O), Leipzig, Valencia, Papillion, and Accuboost applicators. Static-shielded LDR sources such as eye plaques are commercially available, while the CivaSheet™ (CivaTech Oncology, Inc., Durham, NC) (Figure 1A) [58,63,133] are in ongoing clinical trials.

Limitations

The limitations of this study include publication bias and low numbers of clinical studies for dynamic techniques. As many of these studies relied on simulations of patients already treated, there lies the possibility of selection bias for the patients that would benefit the most from IMBT, or only reporting the plans with the most favorable outcomes. This study also was unable to perform a meta-analysis of the available data due to the heterogeneity of the reported outcomes of the studies - specifically the dosimetric outcomes reported for simulated plans. Ideally at least two dosimetric measures should be reported per each specific clinical outcome - whether toxicity or tumor control - which the technique aims to improve upon relative to currently employed techniques. Currently for most IMBT techniques there are not enough studies with a large enough patient population, in the same context, and compared to the same conventional BT standard in order to make valid comparisons. In addition, these studies often used different dosimetric outcomes measures, some of which have not been linked to clinical outcomes.

Future Investigations

What is lacking from the current literature for pre-clinical techniques is the move to larger numbers of simulated plans per study (only 7 studies performed ≥20 simulated plans [17,21,23,26,28,30,65]), methods which preclude the possibility of selection bias of the plans simulated, and more direct comparisons to conventional BT. These studies should report dosimetric results associated with specific clinical outcomes in terms of disease control and sequelae, as well as planning and delivery times. They will need to have large enough patient populations to be powered to detect the expected effect size and should report the statistical

significance of their results. More studies of feasibility in terms of CT/MRI compatibility, optimal shield/source materials, planning algorithms, and applicator design are warranted. Especially in the case of dynamic IMBT techniques in prototype/early clinical phases, more studies of feasibility in terms of workflow and commissioning [5,12,58,97,98] are needed to address practical barriers to clinical implementation. The increased degrees of freedom and mechanical complexity require studies addressing potential sources of error in dosimetry and treatment errors due to shield mispositioning [41,65-69,76,78,79]. Dynamic techniques will need studies demonstrating safety and efficacy in clinical implementation and ability to meet FDA requirements for approval of novel applicator designs. The focus in terms of disease site should be on pathologies which could stand to benefit from decreasing OAR doses, or from dose escalation (but are currently prevented from escalation due to OAR constraints).

V. CONCLUSION

IMBT is a promising treatment modality which can decrease dose to clinically significant OARs by 5.1-68.2% and increase target coverage by 18.6-71.6% relative to conventional BT, depending on the specific disease site and IMBT method employed. Review of the current literature has demonstrated that IMBT is consistently capable of reducing dose to OARs and may possibly allow for dose escalation in circumstances where that may be beneficial such as cervical cancer. Due to the increased degrees of freedom, complexity, and partial shielding associated with IMBT – these plans typically take longer to optimize and deliver than conventional BT plans. The testing of novel applicators, optimal source/shield materials, dose calculation and planning algorithms, and phase I and II clinical trials are all areas for possible future investigations.

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680 **Appendix A. Supplementary Data**

681 Supplementary Data associated with this article, including flowchart of database searches per

682 PRISMA protocol and exhaustive MeSH terms list, can be found in the online version at

683 (http://XXXXXXXX).

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Table and Figure Legends:

Figures

Figure 1- Illustrations of IMBT Techniques

'Dynamic' vs 'Static' IMBT distinguishes between approaches in which the shield does or does not move relative to the source or surrounding tissues during BT delivery. 'Shielded-source' vs 'Shielded-applicator' related to whether the shield is directly associated with the source or is part of the applicator. A) CivaSheet, B) Eye Plaque, C) LDR seeds, D) Shielded SAVI, E) Shielded Ovoid, F) Henschke Ovoid, G) ICMA, H) Accuboost Cup- or D-shaped applicator, I) Papillion, J) Leipzig, K) DirMBT – applications of the same principle optimized for Cervix, L) Rectum, and M) Breast, N) Partially shielded source, O) Interstitial needle, P) DMBT, Q) S-RSBT (single), R) D-RSBT (multiple), S) P-RSBT (Paddles advance/retreat from field), and T) H-RSBT (key enters keyway and shield spins as it is advanced).

Figure 2- PROSPERO Flow Chart for Systematic Literature Search [139]

Collection, inclusion, and exclusion process of systematic literature search adhered to PROSPERO guidelines.

Abv.: AAPM- American Association of Physicists in Medicine, ABS- American Brachytherapy Society, ASCO - American Society of Clinical Oncology, ASTRO - American Society for Radiation Oncology, PDQ – Physician Data Query.

Tables

Table 1- Systematic Search Results Summary

*= Some studies investigated multiple IMBT techniques and were counted in multiple categories. *Abv.*: DirMBT= Direction-Modulated Brachytherapy, DMBT=Dynamic Modulated Brachytherapy, ICMA= Intracavity Mold Applicator, RSBT= Rotating-Shield Brachytherapy, SAVI= Strut-Adjusted Volume Implant.

Table 2- Demographics of Peer Reviewed Articles on IMBT

*=Either number of plans simulated, or patients treated

Abv.: DirMBT- Direction Modulated Brachytherapy, DMBT- Dynamic Modulated Brachytherapy, eBT- Electronic Brachytherapy, IMBT- Intensity Modulated Brachytherapy, kVp- Kilovoltage Peak, REAS- Rapid Emission Angle Selection, RSBT=Rotating-Shield Brachytherapy, SAVI- Strut-Adjusted Volume Implant. All shield materials/isotopes per their periodic table symbols.

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Table 1 - Systematic Search Results Summary

Disease Site	Total	Inclusion	Exclusion
Breast	22	7	15
Cervical	58	31	27
Oculocutaneous	20	10	10
Prostate	104	6	98
Rectal	64	16	48
No Specific Disease Site/Multiple/Other	168	8	160
Total	436	78	358

Technique					
Static Shielding	Shielded Applicator	Tandem and Ovoids	56	9	47
		Cylinders	15	9	6
		SAVI	4	1	3
		ICMA	5	5	0
		Cup or D-shaped	30	16	14
		DirMBT	11	9	2
	Shielded Source		41	12	29
Dynamic Shielding	Dynamic applicator	RSBT	20	15	5
		DMBT	15	2	13
	Dynamic source		239	6	233
	Total		436	84*	352

*= Some studies investigated multiple IMBT techniques and were counted in multiple categories. Abbreviations: DirMBT= Direction-Modulated Brachytherapy, DMBT=Dynamic Modulated Brachytherapy, ICMA= Intracavity Mold Applicator, RSBT= Rotating-Shield Brachytherapy, SAVI= Strut-Adjusted Volume Implant.

Table 2 - Demographics of Peer Reviewed Articles on IMBT

Disease Site	Technique	Technique subcategory	Authors	Year	IMBT to conventional BT comparison	IMBT to IMBT comparison	Development stage	N of Study*	Source/High Z material
Breast	Static Shielding	Shielded Source	Lin et al. & Lin (Thesis)	2008, 2006	*		Simulation	1	I-125/ 0.18mm Au
		Shielded applicator (DirMBT, SAVI)	Webster (Thesis)	2014	*	*	Simulation	36	Ir-192/ 8-10mm W alloy
		Shielded Applicator (Cup or D-shaped)	Hamid et al	2012		*	Clinical use‡	146	Ir-192/W alloy
			Khanal, S.	2013	*	*	Simulation‡	25	Ir-192/W alloy
			Hepel et al	2014		*	Clinical use‡	40	Ir-192/W alloy
			Schuster et al	2016			Clinical use‡	518	Ir-192/W alloy
	Dynamic Shielding	No Specific applicator design	Shi et al	2010	*		Simulation	10	eBT 50kVp / Not Specified
Cervical	Static Shielding	Shielded Applicator (Tandem and Ovoid)	Weeks	1991			Prototype	-	N/A / W Alloy
			Weeks & Montana	1997	*		Prototype	-	Cs-137/W
			Price et al	2005, 2006, 2009	*	*	Dosimetry	-	Cs-137 (LDR), Ir-192 (HDR)/ 5-18mm Densimet-17 or HM3000 1.5-2.1mm
			Lakshminarayanan et al	2010	*		Dosimetry	-	Cs-137, Ir-192/ W 0.8 cm
			Adamson et al	2012	*		Simulation	1	Cs-137/Au 1.0-1.3mm
			Kemp (Thesis)	2012	*		Simulation	18	Cs-137/ Densimet-17
			Heredia (Thesis)	2013			Dosimetry	-	Pd-103/Os 0.03mm
		Shielded Applicator (Cylinder)	Watanabe et al (3D look up tables)	1998, 1998			Simulation	N/A and 20	Ir-192/ W and Ir-192/W alloy
			Solboda & Wang	1998	*		Dosimetry	-	Cs-137/ Stainless steel
			Sureka	2006	*		Dosimetry	-	Ir-192/ W, Pb, or Au
			Zwierzchowski et al	2016			Dosimetry	-	Ir-192/W
		Shielded Applicator (DirMBT)	Han et al	2014, 2016	*		Simulation, Prototype	15, 45	Ir-192/ 5.5-6.4mm (W, Ni, & Cu Alloy)
			Soliman et al	2016			Prototype	-	Ir-192/ 5.5-6.4mm (W, Ni, & Cu Alloy)
			Safigholi et al	2017	*	*	Simulation	45	Ir-192, Yb-169, and Co-60/ W
			Tho et al	2017			Prototype	-	Ir-192/ 5.5-6.4mm (W,

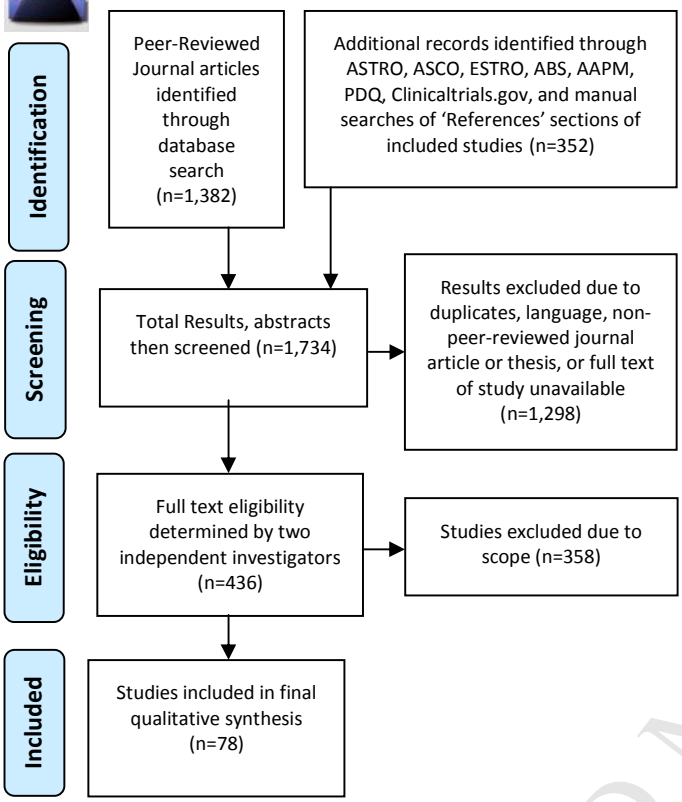
			Elzibak et al	2017			Prototype	-	Ni, & Cu Alloy) Ir-192/ 5.5-6.4mm (W, Ni, & Cu Alloy)
			Safigholi et al (collapsed cone engine)	2018	*		Prototype, dosimetry	-	Ir-192/ 5.5-6.4mm (W, Ni, & Cu Alloy)
			Safigholi et al (optimal shield materials)	2018	*	*	Simulation, Prototype	12	Ir-192/Ta, W, Au, Re, Os, Pt, Ir, or Tungsten alloy
	Dynamic Shielding	Shielded Applicator (RSBT)	Michael Price (Thesis)	2008	*		Simulation, Prototype	1	Ir-192/Densimet-17 tungsten alloy
			Yang et al	2013	*		Simulation	5	eBT 50kVp/ W
			Liu et al. (REAS)	2013		*	Simulation	2	eBT 50kVp / 0.5mm W
			Liu et al. (D-RSBT)	2013	*	*	Simulation	5	eBT 50kVp / 0.5mm W
			Liu et al.	2014, 2015		*	Simulation	5, 5	eBT 50kVp / 0.5mm W
			Dadkhah et al.	2015		*	Simulation	5	eBT 50kVp / 0.5mm W
			Tian et al	2016		*	Simulation	1	Ir-192/ W, variable diameters
			Cho et al	2017		*	Simulation	5	eBT 50kVp / 0.5mm W
Oculocutaneous	Static	Shielded Source (Eye plaque)	Mameghan et al	1992			Clinical use‡	53	I-125/Stainless steel 0.5mm
			Chaudhari et al	2008			Dosimetry	-	I-125/Au 0.5mm
			Melhus	2008			Dosimetry	-	Cs-131, I-125, pd-103/Au alloy 0.5mm
			Zhang	2010			Dosimetry	–	Cs-131, I-125/Au or Au alloy 0.5mm
			Gagne & Rivard	2013			Dosimetry	-	Cs-131, I-125, pd-103/Au alloy 0.5mm
			Böker et al	2018			Clinical use‡	136	Ru-106/Ag 0.7mm
		Shielded Applicator (Cup or D-shaped)	Coquard et al	2017			Clinical use‡	14	eBT/Stainless Steel
			Arenas et al	2015			Clinical use‡	114	Ir-192/W
			Gauden et al	2013			Clinical use‡	200	Ir-192/W
			Kasper et al	2013			Clinical use‡	16	Ir-192/W
Prostate	Dynamic Shielding	Shielded Source (Interstitial needles)	Ebert	2006	*		Simulation	1	Ir-192 / Not Specified
			Adams et al.	2014	*		Simulation, prototype	1	Gd-153/ 0.5-0.6mm Pt
			Xing Li (Thesis)	2015	*		Simulation, Prototype	1	eBT/Ti or CoCr ~1mm (Cervix), Gd-153/Pt 0.5mm (prostate)

			Dadkhah et al.	2017	*		Simulation	1	Gd-153/ 0.5-0.6mm Pt
			Gorbani et al	2017			Dosimetry	-	Gd-153/ 0.5-0.6mm Pt
			Adams et al.	2018	*	*	Simulation	26	Gd-153 or Ir-192/ 0.5-0.6mm Pt
Rectal	Static Shielding	Shielded Applicator (ICMA)	Poon et al	2006, 2008			Clinical use	N/A and 40	Ir-192/ 8mm W or Pb
			Yan et al	2008		*	Clinical use	42	Ir-192/ 8mm W or Pb
		Shielded Applicator (Cylinder)	Hansen et al	2006	*	*	Prototype	-	Ir-192/ Pd and W
			Jakobsen et al	2006, 2012			Clinical use	50, 243	Ir-192/ Pb
		Shielded Applicator (Cup or D-shaped)	Papillion et al	1984, 1989, 1990			Clinical use‡	245, 62, 310	eBT/Stainless Steel
			Roth et al	1989			Clinical use‡	91	eBT/Stainless Steel
			Frin et al	2016			Clinical use‡	112	eBT/Stainless Steel
			Myint et al.	2017, 2018			Clinical use‡	200, 83	eBT/Stainless Steel
			Gerard et al	1996, 2018			Clinical use‡	101, 74	eBT/Stainless Steel
			Dunstan et al	2018			Clinical use‡	7	eBT/Stainless Steel
			Bellezo et al	2018		*	Prototype, dosimetry	-	Ir-192/ W
	Dynamic Shielding	Dynamic applicator (DMBT, ICMA)	Webster et al.	2012	*		Simulation	13	Ir-192/ 10-30mm Tungsten alloy
			Webster et al	2013	*		Simulation	13	Ir-192/ 16mm Tungsten alloy
Other, Multiple or no specific disease site	Static Shielding	Shielded Source (Civa)	Aima et al	2015, 2018	*		Dosimetry	-	Pd-103/ 0.05mm Au
			Rivard	2017			Dosimetry	-	Pd-103/ 0.05mm Au
			Cohen et al	2017			Clinical use	4	Pd-103/ 0.05mm Au
			Seneviratne et al	2018			Clinical use	1	Pd-103/ 0.05mm Au
		Shielded Applicator (Cylinder)	Lymperopoulou et al	2004	*		Dosimetry	-	Ir-192/ W
	Dynamic Shielding	Dynamic Source	Kim et al.	2003	*		Dosimetry	-	Sr-90 or Y Novoste Beat-Cath/ 0.64mm W or Stainless Steel
		Dynamic Applicator	Ebert	2002	*		Dosimetry	-	I-125, Ir-192/ Not Specified

*=Either number of plans simulated or patients treated, ‡=Comercially avaiable at time of publication

Abv.: DirMBT- Direction Modulated Brachytherapy, DMBT- Dynamic Modulated Brachytherapy, eBT- Electronic Brachytherapy, IMBT- Intensity Modulated Brachytherapy, kVp- Kilovoltage Peak, REAS- Rapid Emission Angle Selection, RSBT=Rotating-Shield Brachytherapy, SAVI- Strut-Adjusted Volume Implant. All shield materials/isotopes per their periodic table symbols.

Figure 2 - PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Abbreviations

AAPM- American Association of Physicists in Medicine
ABS- American Brachytherapy Society
ADOS- asymmetric dose–volume optimization with smoothness control
APBI – Accelerated Partial Breast Irradiation
ASTRO - American Society for Radiation Oncology
ASCO - American Society of Clinical Oncology
BT – Brachytherapy
CAD- Coronary Artery Disease
CTV – Clinical Target Volume
D-RSBT - Rotating-shield Brachytherapy
D_{90} = Volume receiving 90% of prescription dose
DHI- Dose Homogeneity Index
DirMBT- Direction-Modulated Brachytherapy
DMBT- Dynamic-Modulated Brachytherapy
DSO= dose–surface optimization
EBRT- External Beam Radiation Therapy
EBSCO- Elton Bryson Stephens Company
eBT – Electric source BT
ESTRO - European Society of Radiotherapy and Oncology
HDR – High-dose Rate
HDR-BT - High-Dose Rate Brachytherapy
HR-CTV= High Risk Clinical Target Volume
ICBT = Conventional Intracavity Brachytherapy
ICBT + SI = Conventional Intracavity Brachytherapy and Supplementary Interstitial
IGRT- image-guided radiation therapy
IMBT – Intensity Modulated Brachytherapy
IPSA= inverse-planning with simulated annealing
LDR- Low Dose-Rate
MeSH – Medical Subject Heading
NIH – National Institute of Health
OAR- Organ At Risk
PDQ – Physician Data Query
P-RSBT – Paddle-based Rotating-shield Brachytherapy
PRISMA - Preferred Reporting Items for Systemic reviews and Meta Analyses
RSBT - Rotating-shield Brachytherapy
SAVI - Strut-Adjusted Volume Implant
SBRT- stereotactic-body radiation therapy
S-RSBT – Single-shield Rotating-shield Brachytherapy
TG43 – Task Group #43 (American Association of Physicists in Medicine**)**
VMAT- volumetric-modulated arc therapy
WBI- Whole Breast Irradiation

Supplementary Materials

For all searches "search terms" included the following:

- Intensity Modulated Brachytherapy
- Dynamic Modulated Brachytherapy
- Direction Modulated Brachytherapy
- Rotating Shield Brachytherapy
- HDR Brachytherapy Shielding
- High Dose Rate Brachytherapy Shielding
- 3D Conformal Brachytherapy Shielding

1. Database Search Parameters
    a. Pubmed
        i. (((((("intensity modulated brachytherapy"[Text Word] OR "dynamic modulated brachytherapy"[Text Word]) OR "direction modulated"[Text Word]) OR "rotating shield brachytherapy"[Text Word]) OR "high dose rate brachytherapy intensity"[Text Word]) OR "3d conformal hdr brachytherapy"[Text Word]) AND ("1980/01/01"[PubDate] : "3000"[PubDate])
    b. Medline
        i. (((((("intensity modulated brachytherapy"[Title/Abstract] OR "dynamic modulated brachytherapy"[Title/Abstract]) OR "direction modulated"[Title/Abstract]) OR "rotating shield brachytherapy"[Title/Abstract]) OR "3d conformal hdr brachytherapy"[Title/Abstract]) OR (High[All Fields] AND Dose[All Fields] AND ("J Rehabil Assist Technol Eng"[Journal] OR "rate"[All Fields]) AND ("brachytherapy"[MeSH Terms] OR "brachytherapy"[All Fields]) AND Shielding[Title/Abstract])) AND ("1980/01/01"[PDAT] : "3000"[PDAT])
    c. Google Scholar
        i. Anywhere in the article, with all the words 'Intensity Modulated Brachytherapy OR Dynamic Modulated Brachytherapy OR Direction Modulated Brachytherapy OR Rotating Shield Brachytherapy OR High Dose Rate Brachytherapy Shielding OR 3D Conformal Brachytherapy Shielding'. No patents or citations included, Published 1980-2018.

d. Cochrane Library
    i. Search settings include 'Boolean/Phrase', 'Apply related words', 'Apply equivalent subjects', and 'Date 1980-2018'. Sources included Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Applied Science & Business Periodicals Retrospective: 1913-1983 (H.W. Wilson), Applied Science & Technology Source, Cochrane Clinical Answers, eBook Collection (EBSCOhost), E-Journals, General Science Full Text (H.W. Wilson), History of Science, Technology & Medicine, Library Literature & Information Science Full Text (H.W. Wilson), Library, Information Science & Technology Abstracts, UCF Libraries Catalog. All search terms where searched simultaneously under the 'AB Abstract' and 'OR' tabs selected.
e. UCF Search Engine
    i. 'AB Abstract' selected for search terms searched individually. 'peer-reviewed publications' and 'Find all of my search terms' selected with 'full text online' and dates of 1980-2018.