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The American Brachytherapy Society consensus statement for electronic brachytherapy

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ABSTRACT

PURPOSE: Brachytherapy is utilized in the treatment of many different malignancies; although traditionally performed with low-dose-rate or high-dose-rate techniques, more recently, electronic brachytherapy (EB) has emerged as a potential alternative. At this time, there are no evidence-based guidelines to assist clinicians in patient selection for EB and concerns exits regarding differences in dosimetry as compared to traditional brachytherapy techniques. As such, the American Brachytherapy Society appointed a group of physicians and physicists to create a consensus statement regarding the use of EB.

METHODS AND MATERIALS: Physicians and physicists with expertise in brachytherapy created a site-directed consensus statement for appropriate patient selection and utilization of EB based on a literature search and clinical experience.

RESULTS: EB has been utilized to deliver accelerated partial breast irradiation with, thus far acceptable local control and toxicity rates including a randomized trial that used EB to deliver intraoperative radiotherapy; however, prospective data with large patient numbers and long-term follow up are needed. Increasing numbers of patients have been treated with EB for nonmelanomatous skin cancers; although, preliminary data are promising, there is a lack of data comparing EB to traditional radiotherapy techniques as well as a lack of long-term follow up. For treatment of the vaginal cuff with EB, small retrospective studies have been reported without long-term follow up.

CONCLUSIONS: In light of a randomized trial in breast showing higher rates of recurrence and the lack of prospective data with mature follow up with other sites, as well as concerns regarding dosimetry, it is not recommended that EB be utilized for accelerated partial breast irradiation, nonmelanomatous skin cancers, or vaginal cuff brachytherapy outside prospective clinical trials at this time.

Keywords: Radiation therapy; Electronic brachytherapy; Breast cancer; Skin cancer; Endometrial cancer; Cervical cancer

Introduction

Brachytherapy represents a combination of techniques that can be utilized to deliver radiation therapy to the surface/superficially (e.g. nonmelanomatous skin cancers, vaginal cuff) or to deeper targets (e.g. breast, prostate); because of its versatility, brachytherapy has been incorporated into treatment paradigms for multiple disease sites as monotherapy or in conjunction with external beam radiation therapy. Traditionally, brachytherapy has been delivered with radioactive isotopes that can be categorized as permanent or temporary and as low-dose-rate/high-dose-rate depending on the technique and isotope selected. More recently, electronic brachytherapy (EB) has emerged as an alternative brachytherapy technique for certain disease sites.

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EB offers several unique features compared to traditional brachytherapy including lower energy (typically < 120 kVp) photons as compared to isotope-based treatment and therefore, reduced shielding needs (1). However with the use of lower energy photons, dose distributions will be different than with traditional brachytherapy techniques with the superficial photons used with EB associated with less deep coverage and higher surface doses. These differences limit the extrapolation of data from traditional brachytherapy techniques to EB with respect to clinical outcomes, toxicity profiles, and indications. In addition, traditional brachytherapy has routinely been studied in Phase III trials; however, there is a lack of randomized and prospective data regarding the use of EB at this time. Previously, the American Brachytherapy Society, in conjunction with the American College of Radiology, published a practice parameter for electronically generated low-energy radiation sources (1). This statement presented information on clinical evaluation for patients undergoing EB as well as treatment planning and delivery. At this time, we present a consensus statement regarding EB, focusing on current clinical data and provide guidelines for appropriate utilization of EB by disease site.

Methods and Materials

The American Brachytherapy Society Board of Directors appointed a group of physicians and physicists with expertise in brachytherapy to provide a consensus statement on EB. The goals of the project were to provide recommendations based on the data available for each treatment site. A review of the literature with a focus on trials, prospective studies, multi-institutional series, as well as single institution reports addressing clinical outcomes and toxicities with EB was performed inclusive of all publications regardless of year. Key words were used including "electronic brachytherapy, Xoft, Esteya, Intrabeam." Following a discussion, the guidelines were created based on consensus among the authors. Before publication, the consensus statement was approved by the American Brachytherapy Society (ABS) Board of Directors.

Results

Physics of electronic brachytherapy

The American Association of Physicists in Medicine (AAPM) Task Group 152 defines electronic brachytherapy as "a method of radiation therapy using electrically generated x rays to deliver a radiation dose at a distance of up to a few centimeters by intracavitary, intraluminal, or interstitial application, or by applications with the source in contact with the body surface or very close to the body surface (2)." At the time of writing of this report, three electronic brachytherapy units are commercially available: Axxent (Xoft Inc., subsidiary of iCAD Inc., San Jose, CA); Esteya (Elekta AB-Nucletron, Stockholm, Sweden); and INTRABEAM (Carl Zeiss Surgical GmbH, Oberkochen, Germany).

EB units operate in the 50–70 kVp energy range, requiring little shielding and can therefore be used in a wide variety of settings including examination rooms and standard operating rooms. TG-152, which outlines safety requirements for units of this category, recommends that for units operating at less than 60 kVp, portable or localized radiation shielding be available in the room for the protection of staff. For this reason, units that operate at the lower kV may have the added benefit of being portable, as the shielding required can be transported to the treatment room. Other units, operating at higher peak voltage, may require added shielding and safety considerations. Unlike isotopic brachytherapy, electronic brachytherapy is not regulated by the Nuclear Regulatory Commission (NRC). However, local regulations may apply and users should consult their local hospital-based radiation safety committee. Table 1 offers a summary of the main characteristics for these units (3–8).

Dosimetric concerns

Although the difference between traditional isotopic brachytherapy and EB seems semantic at first glance, the dose calculation in tissue, and its clinical implications are still being studied. Although EB has been available for over 2 decades, there are no consensus dosimetry data available for these units. Further clinical trials may be needed to

Table 1
Summary of basic characteristics of electronic brachytherapy compared to commonly used radioisotopes

Unit	Axxent	Esteya	Intrabeam	I-125	Ir-192 HDR
Vendor	Xoft Inc-iCad Inc	Elekta AB-Nucletron	Carl Zeiss Surgical GmbH	Various seed manufacturers	Varian, Elekta AB-Nucletron Eckert Ziegler Bebig
Portability	Yes	No	Yes	Yes	No
Shielding requirement	Local or portable	Portable (some room shielding may be required)	Local or portable	Local or portable	Shielded treatment vault
Common clinical applications	Skin, Breast, Vaginal cylinders, IORT	Skin only	Breast, Skin, Brain, IORT	Various sites	Various sites Incl. IORT
Energy	50 kVp	70 kVp	50 kVp	28 keV	380 keV
Dosimetry references	Rivard *et al.* 2006	Garcia-Martinez *et al.* 2014	Eaton 2012 AAPM TG-186	AAPM TG-43	AAPM report 229

establish clinical guidelines and consensus regarding whether to modify the prescription with EB to account for potential differences in RBE.

Dose calculations for the Esteya and Intrabeam are based on vendor-provided data. For the Xoft S700 source, TG-43 parameters have been determined by Rivard *et al.* (7). The kilovoltage units are characterized by a relatively wide spectrum of low-energy photons for which water-based TG-43 formalism may result in significant differences in depth dose estimates in tissue. Although AAPM TG-186 has proposed methodology to address this challenge, this is still an area of research (6). In addition, Brenner *et al.* have reported on the increased relative biological effectiveness of low-energy photons (9). This and the steep depth dose curve, associated with these X-ray devices, may preclude prescription depths of more than a few millimeters in tissue; this is because with such dose curves, prescribing to a deep target volume is associated with high surface doses. This may be of clinical significance in the case of vaginal cuff brachytherapy, for example, where prescription is often at a depth of 5 mm, resulting a higher surface dose with EB than traditional Ir-192-based high dose rate (HDR) treatments (10). In the case of breast brachytherapy, where prescription with balloon-type applicators is typically at 10 mm from the surface of the applicator, that effect is greater yet. To prevent the toxicity associated with increase surface dose, the prescription depth for EB is often specified at the surface of the applicator, resulting in turn a lower dose to tissue at depth. For example, for a 2 cm breast Mammosite-type applicator employing the Xoft Axxent source, the dose at 1 cm form the surface is calculated to be approximately 28% of the surface dose as compared to 100% with HDR (3). Finally, with EB there are less widely available imaging protocols for applicator evaluation and dosimetry as compared to HDR brachytherapy.

Process

With regard to the process of performing EB, the American College of Radiology/ABS guideline, previously published, details clinical evaluation, treatment goals, treatment planning, and delivery of EB as well as follow up parameters (1). This guideline also provides detailed descriptions for personnel qualifications for EB as well as equipment specifications, patient/personnel safety, educational programs, and documentation. As such, separate recommendations are not provided.

Clinical sites

Breast cancer

Adjuvant radiation therapy following breast-conserving surgery represents the standard of care approach for most women with significant reductions in local recurrences as well as breast cancer mortality as compared to surgery alone (11). Although initial studies comparing mastectomy and breast conservation utilized conventionally fractionated whole breast irradiation (WBI), hypofractionated WBI has been shown in several randomized trials to be equivalent to conventionally fractionated WBI and is recommended by current evidence-based guidelines (12). Accelerated partial breast irradiation (APBI) represents an alternative to WBI that can be delivered with interstitial brachytherapy, applicator-based brachytherapy, or external beam techniques. Currently 5–10 year prospective randomized outcomes are available documenting excellent clinical outcomes comparable to WBI, for appropriately selected patients. Evidence-based guidelines are available and support the use of these techniques off-protocol (13, 14).

EB, while representing a partial breast technique, is different than other APBI techniques and as such guidelines for utilizing APBI should not be used for the treatment of patients with EB (14, 15). It should be noted that low-energy electronic sources are used intraoperatively and are discussed in the adjoining ABS intraoperative radiation therapy (IORT) consensus statement as well as the ABS partial breast irradiation consensus statement (1, 14). Although intraoperative strategies (including one using low-energy photons, consistent with EB) have been studied in randomized trials, both studies demonstrated higher rates of local recurrence (though within noninferiority threshold for TARGIT trial), inconsistent with other partial breast irradiation (PBI) trials. In addition, the TARGIT trial lacks long-term follow up, with a median follow up of less than 3 years. Finally, randomized trials evaluating APBI as compared to WBI did not allow for EB or intraoperative radiation therapy and as such it is not recommended for use outside of prospective studies by current guidelines (16, 17).

Outside of these trials, the use of EB to deliver partial breast irradiation has been evaluated both intraoperatively (single fraction) as well as using fractionated partial breast irradiation (18–20). When delivering fractionated PBI, traditional APBI applicators, which have been well studied, can be utilized (21); however, it is important to recognize the differences as compared to HDR, despite the same applicators being used. For example, with brachytherapy techniques (e.g. Interstitial, applicator), 100% of the prescription dose is given to a minimum of 1 cm from the cavity surface and with external beam techniques this can be even greater. For intraoperative EB, dose is prescribed to the surface of the lumpectomy cavity resulting in only 25–30% of the prescription dose delivered at depth (14, 22). This is important, as data have found that 90% of residual disease following lumpectomy (when present) is within 1 cm of the cavity (23). Unlike intraoperative EB, postoperative fractionated PBI using EB is typically prescribed in a standard fashion to 1 cm from the cavity surface. However, these results are in a substantially higher cavity surface dose compared to established brachytherapy PBI techniques (24). The clinical impact of this, if any, is not fully elucidated.

The largest series utilizing EB to date evaluated 984 women with early-stage breast cancer (1000 cancers),

who underwent lumpectomy followed by EB; with a median follow up of 36 months, the 4-year local recurrence rate was 3.9%; these results have been confirmed with smaller series as well (25–31). With respect to safety and toxicity outcomes, Epstein *et al.* evaluated 702 patients and found a 21% rate of acute complications with 13% of patients having chronic complications including seromas, fibrosis, and skin changes. In addition, only 5% of patients had significant complications (defined as complications other than Grade 1 erythema, fibrosis, or hyperpigmentation) (27). Smaller studies have confirmed appropriate safety end points and treatment tolerability with a retrospective series finding similar dosimetry to HDR plans (30, 31). Limited long-term follow up is available with an abstract from Dickler *et al.* identifying 68 patients and a 6% local recurrence rate at 5 years, higher than that seen with alternative PBI techniques (32). Similarly, a series of 184 patients with a follow up of 55 months had a 5.4% recurrence (33). Finally, although EB has been suggested as a cost savings technique, it is important to recognize that if it is associated with higher rates of recurrence (as seen with low-energy IORT), then the cost savings derived may not be accurate (34, 35). Currently, clinical studies are underway to further evaluate outcomes with EB following lumpectomy.

Recommendation. Consistent with the ABS consensus statement for ABPI, EB should not be offered to patients outside of prospective clinical registries or trials as IORT or fractionated partial breast irradiation, regardless of technique utilized (Table 2).

Future directions. Data with large numbers of patients and mature follow up of 5 years or longer are needed. The randomized TARGIT trial is ongoing further follow up with outcomes expected in the years to come. EB delivered as fractionated PBI with applicators should also be evaluated with prospective studies.

Skin cancers

Skin cancer represents the most common cancer in the United States; nonmelanomatous skin cancers ([NMSC], basal cell carcinomas [BCC], and squamous cell carcinomas [SCC]) are the most common with multiple treatment techniques available including surgery and radiotherapy (36). The most commonly utilized radiation therapy techniques include electron therapy, megavoltage photon therapy, brachytherapy, and superficial/orthovoltage techniques (37). With respect to brachytherapy, significant clinical data exist supporting the role of brachytherapy for small skin cancers (38).

A growing set of literature exists regarding the use of EB for NMSC, though follow up remains short. Initial studies demonstrated the feasibility of the technique with limited acute toxicity (39). Updated outcomes at 1 year confirmed no recurrences and toxicity profiles that were consistent with other radiotherapy techniques, including no Grade 3 toxicities (40). In a second series from Paravati *et al.*, which evaluated 127 patients (154 lesions) and with a median follow up of 16 months, the local recurrence rate was 1.3%; however, the Grade 3 acute dermatitis rate was 13% with no late Grade 3 toxicities (Grade 2: 5.8%) (41). Similar results are noted from two prospective studies of 20 patients each as well as additional series (42–45). The largest series to date is a pooled analysis of 1259 patients (1822 lesions) from six publications, treated between 2009 and 2014; patients were treated to 40–45 Gy in 3–8 fractions with 95% of lesions being BCC/SCC. Most patients had follow up less than 1 year (n = 926) with only 47 patients having follow up beyond 3 years; the recurrence rate was 0.97% (46).

It should be noted that although these data are important, there are limited data comparing EB with other radiotherapy or surgical techniques; Patel *et al.* evaluated 369 patients (188 received EB, 181 Mohs surgery) in a matched pair cohort study. Median age was 81 years old for the EB cohort and 77 for the Mohs cohort; with 3.4 year mean follow up, no difference in rates of recurrence were noted with similar cosmetic outcomes (47). However, further data comparing outcomes to surgery and radiotherapy techniques are needed. In addition, outcomes in younger patients are needed as they are underrepresented in previously published series.

Concerns

There has been a rapid increase in the use of EB for the treatment of NMSC, but without meaningful comparison to standard radiotherapy techniques, surgical techniques, and without long-term follow up data (48). When employing EB, the maximum prescription depth is typically less than 5 mm (standardly 3 mm) to maintain a safe surface dose; for example, the surface dose with a 3 mm prescription

Table 2
Summary of recommendations for electronic brachytherapy by treatment site

	Recommendation	Future direction
Breast cancer (IORT)	Not recommended outside of clinical registry or trial	Randomized and prospective data; mature follow up
Breast cancer (fractionated partial breast irradiation)	Not recommended outside of clinical registry or trial	Randomized and prospective data; mature follow up
Nonmelanomatous skin cancers	Not recommended outside of clinical registry or trial	Randomized and prospective data; mature follow up
Vaginal cuff	Not recommended outside of clinical trial	Randomized and prospective data; mature follow up

depth is between 124% and 152% using a 2 cm applicator (49). In addition, a particular concern is the uncertainty of tumor depth and whether often used clinical estimates, without routine use of imaging or computed tomography dosimetry, ensures adequate target coverage for what are assumed to be shallow lesions but may in fact be deeper and more infiltrative tumors (50–52). The lack of standardized dosimetry (as compared to EBRT, brachytherapy) and planning limits the ability to evaluate dose once delivered as a means for quality assurance as well.

Although the matched pair cohort discussed above found no difference in recurrence rates with a median follow up of 3.4 years, further follow up is needed as the median time to recurrence of a primary NMSC is 2–5 years (47, 53). In addition, Linos *et al.* addressed the concern regarding the rapid increase in the use of EB for skin cancer, finding a 20-fold increase in the use of a specific billing code from 2011 to 2014, based on 98% of the cases using the code involving skin EB. The article notes concern regarding this increase because of a ''lack of efficacy and safety data'' (48); this was supported by a commentary from Haffty *et al.* with the American Society of Radiation Oncology (ASTRO) supporting modifications of the CPT code to avoid potential abuse. The commentary also notes that long-term data regarding EB are needed (54).

Recommendation. At this time, there are growing data with respect to EB and NMSC; however, there is a lack of comparative data to traditional treatments, limited data with long-term follow up, and a need for younger patients in studies before generalizing recommendations. Although data can be extrapolated from orthovoltage experiences with NMSC, in light of the large numbers of patients diagnosed with NMSC, prospective studies with larger numbers of patients undergoing EB should be performed. Until mature outcomes are available, treatment should be performed on clinical registry or trial at this time (Table 2). Recommendations for dosimetry are presented in the previous ABS skin cancer guidelines (49).

Future directions. Further data with mature follow up are required; in addition, studies evaluating methods to optimize EB in treating skin cancer are ongoing including the use of ultrasound to assess the depth of lesions (51, 55). It is imperative that EB studies focus on consistent planning techniques as well, to ensure appropriate target coverage.

Gynecologic cancers

Vaginal brachytherapy is routinely indicated for patients with endometrial and cervical cancers as the sole form of radiation therapy (following surgery) or in conjunction with external beam radiotherapy (56, 57). Currently, this treatment is most commonly delivered with HDR brachytherapy. Dosimetric studies have demonstrated the feasibility to deliver vaginal cuff EB; Mobit *et al.* found lower doses to organs at risk with the exception of the rectum with EB (58). In addition, EB was associated with higher vaginal surface doses than HDR brachytherapy (10). At this time, limited clinical data are available regarding the use of EB to deliver vaginal cuff brachytherapy (59–61). Kamrava *et al.* published a series of 16 patients (13 endometrial, 3 cervical) undergoing postoperative EB to the vaginal cuff. With a median follow up of 20.5 months, the local and locoregional control were 94%. With respect to toxicity, no Grade 4–5 events were noted and the Grade 2 + toxicity rate was 25% (59). Similarly, Dickler *et al.* published a series of 15 patients with endometrial cancer treated with EB; low rates of toxicity were noted without Grade 3–4 toxicities though follow up was short (60). Finally, it should be noted that EB was not used on previous GOG/RTOG gynecologic cancer trials as a form of approved brachytherapy.

Recommendation. At this time, there is a paucity of data with respect to utilizing EB for gynecologic cancers. It is not recommended that EB be used to deliver vaginal cuff brachytherapy outside of a clinical trial (Table 2).

Future directions. Randomized data comparing EB to alternative well-established brachytherapy techniques are unavailable at this time. Moving forward, such studies are needed with mature follow up to evaluate the role of EB for gynecologic cancers.

Conclusions

Electronic brachytherapy represents an innovative technique to deliver brachytherapy with several potential advantages over current techniques. However, based on currently available data, the use of electronic brachytherapy outside of prospective registry or trial is not recommended for patients with breast cancer, nonmelanomatous skin cancers, or patients with endometrial or cervical cancer requiring vaginal cuff brachytherapy. Future studies are required to compare electronic brachytherapy to traditional radiotherapy and brachytherapy techniques along with longer follow up.

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References

[1] Devlin PM, Gaspar LE, Buzurovic I, *et al*. American College of Radiology-American Brachytherapy Society practice parameter for electronically generated low-energy radiation sources. *Brachytherapy* 2017;16:1083–1090.

[2] AAPM Reports - the 2007 AAPM response to the CRCPD request for recommendations for the CRCPD's model regulations for electronic brachytherapy. Available at: https://www.aapm.org/pubs/reports/detail.asp?docid=157. Accessed October 1, 2018.
[3] Rivard MJ, Davis SD, DeWerd LA, *et al*. Calculated and measured brachytherapy dosimetry parameters in water for the Xoft Axxent X-Ray Source: an electronic brachytherapy source. *Med Phys* 2006;33:4020–4032.
[4] Garcia-Martinez T, Chan JP, Perez-Calatayud J, *et al*. Dosimetric characteristics of a new unit for electronic skin brachytherapy. *J Contemp Brachytherapy* 2014;6:45–53.
[5] Eaton DJ. Quality assurance and independent dosimetry for an intraoperative x-ray device. *Med Phys* 2012;39:6908–6920.
[6] Beaulieu L, Carlsson Tedgren A, Carrier JF, *et al*. Report of the Task Group 186 on model-based dose calculation methods in brachytherapy beyond the TG-43 formalism: current status and recommendations for clinical implementation. *Med Phys* 2012;39:6208–6236.
[7] Rivard MJ, Coursey BM, DeWerd LA, *et al*. Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations. *Med Phys* 2004;31:633–674.
[8] Perez-Calatayud J, Ballester F, Das RK, *et al*. Dose calculation for photon-emitting brachytherapy sources with average energy higher than 50 keV: Report of the AAPM and ESTRO. *Med Phys* 2012;39:2904–2929.
[9] Brenner DJ, Leu CS, Beatty JF, *et al*. Clinical relative biological effectiveness of low-energy x-rays emitted by miniature x-ray devices. *Phys Med Biol* 1999;44:323–333.
[10] Dickler A, Kirk MC, Coon A, *et al*. A dosimetric comparison of Xoft Axxent Electronic Brachytherapy and iridium-192 high-dose-rate brachytherapy in the treatment of endometrial cancer. *Brachytherapy* 2008;7:351–354.
[11] Darby S, McGale P, Correa C, *et al*. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–1716.
[12] Smith BD, Bellon JR, Blitzblau R, *et al*. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* 2018;8:145–152.
[13] Correa C, Harris EE, Leonardi MC, *et al*. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 2017;7:73–79.
[14] Shah C, Vicini F, Shaitelman SF, *et al*. The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation. *Brachytherapy* 2018;17:154–170.
[15] On the road to intraoperative radiotherapy: More 'proceed with caution' signs | cancer network. Available at: http://www.cancernetwork.com/breast-cancer/road-intraoperative-radiotherapy-more-proceed-caution-signs. Accessed October 1, 2018.
[16] Vaidya JS, Wenz F, Bulsara M, *et al*. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383:603–613.
[17] Veronesi U, Orecchia R, Maisonneuve P, *et al*. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. *Lancet Oncol* 2013;14:1269–1277.
[18] Dickler A, Ivanov O, Francescatti D. Intraoperative radiation therapy in the treatment of early-stage breast cancer utilizing xoft axxent electronic brachytherapy. *World J Surg Oncol* 2009;7:24.
[19] Chen SS, Strauss JB, Shah AP, *et al*. Radiation recall reaction with docetaxel administration after accelerated partial breast irradiation with electronic brachytherapy. *Brachytherapy* 2009;8:331–334.
[20] Strauss JB, Dickler A. Accelerated partial breast irradiation utilizing balloon brachytherapy techniques. *Radiother Oncol* 2009;91:157–165.
[21] Shah C, Badiyan S, Ben Wilkinson J, *et al*. Treatment efficacy with accelerated partial breast irradiation (APBI): final analysis of the American Society of Breast Surgeons MammoSite((R)) breast brachytherapy registry trial. *Ann Surg Oncol* 2013;20:3279–3285.
[22] Jones R, Libby B, Showalter SL, *et al*. Dosimetric comparison of (192)Ir high-dose-rate brachytherapy vs. 50 kV x-rays as techniques for breast intraoperative radiation therapy: Conceptual development of image-guided intraoperative brachytherapy using a multilumen balloon applicator and in-room CT imaging. *Brachytherapy* 2014;13:502–507.
[23] Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: A pathologic analysis. *Int J Radiat Oncol Biol Phys* 2004;60:722–730.
[24] Dickler A, Kirk MC, Seif N, *et al*. A dosimetric comparison of MammoSite high-dose-rate brachytherapy and Xoft Axxent electronic brachytherapy. *Brachytherapy* 2007;6:164–168.
[25] Silverstein MJ, Epstein M, Kim B, *et al*. Intraoperative radiation therapy (IORT): A series of 1000 tumors. *Ann Surg Oncol* 2018;25:2987–2993.
[26] Silverstein MJ, Epstein MS, Lin K, *et al*. Intraoperative radiation using low-kilovoltage X-rays for early breast cancer: a single site trial. *Ann Surg Oncol* 2017;24:3082–3087.
[27] Epstein M, Silverstein M, Lin K, *et al*. Acute and chronic complications in breast cancer patients treated with intraoperative radiation therapy. *Ann Surg Oncol* 2016;23:3304–3309.
[28] Lai HW, Liu LC, Ouyang F, *et al*. Multi-center study on patient selection for and the oncologic safety of intraoperative radiotherapy (IORT) with the Xoft Axxent(R) eBx(R) System for the management of early stage breast cancer in Taiwan. *PLoS One* 2017;12:e0185876.
[29] Patel RR, Beitsch PD, Nichols TD, *et al*. Postsurgical treatment of early-stage breast cancer with electronic brachytherapy: Outcomes and health-related quality of life at 1 year. *Am J Clin Oncol* 2013;36:430–435.
[30] Ivanov O, Dickler A, Lum BY, *et al*. Twelve-month follow-up results of a trial utilizing Axxent electronic brachytherapy to deliver intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol* 2011;18:453–458.
[31] Dooley WC, Wurzer JC, Megahy M, *et al*. Electronic brachytherapy as adjuvant therapy for early stage breast cancer: A retrospective analysis. *Onco Targets Ther* 2011;4:13–20.
[32] Dickler A, Ivanov O, Syed AMN, *et al*. Five year results of a multicenter trial utilizing electronic brachytherapy to deliver intraoperative radiation therapy in the treatment of early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2015;93:e24–e25.
[33] Schwartzberg BS, Chin DT, Dorn PL, *et al*. Application of 21-gene recurrence score results and ASTRO suitability criteria in breast cancer patients treated with intraoperative rdiation therapy (IORT). *Am J Surg* 2018;216:689–693.
[34] Patel R, Ivanov O, Voigt J. Lifetime cost-effectiveness analysis of intraoperative radiation therapy versus external beam radiation therapy for early stage breast cancer. *Cost Eff Resour Alloc* 2017;15:22.
[35] Shah C, Badiyan S, Khwaja S, *et al*. Evaluating radiotherapy options in breast cancer: Does intraoperative radiotherapy represent the most cost-efficacious option? *Clin Breast Cancer* 2014;14:141–146.
[36] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
[37] Rong Y, Zuo L, Shang L, *et al*. Radiotherapy treatment for nonmelanoma skin cancer. *Expert Rev Anticancer Ther* 2015;15:765–776.
[38] Ota K, Adar T, Dover L, *et al*. Review: The reemergence of brachytherapy as treatment for non-melanoma skin cancer. *J Dermatolog Treat* 2018;29:170–175.
[39] Bhatnagar A, Loper A. The initial experience of electronic brachytherapy for the treatment of non-melanoma skin cancer. *Radiat Oncol* 2010;5:87.

[40] Bhatnagar A. Nonmelanoma skin cancer treated with electronic brachytherapy: Results at 1 year. *Brachytherapy* 2013;12:134–140.
[41] Paravati AJ, Hawkins PG, Martin AN, *et al*. Clinical and cosmetic outcomes in patients treated with high-dose-rate electronic brachytherapy for nonmelanoma skin cancer. *Pract Radiat Oncol* 2015;5:e659–e664.
[42] Ballester-Sanchez R, Pons-Llanas O, Candela-Juan C, *et al*. Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses. *J Contemp Brachytherapy* 2016;8:48–55.
[43] Ballester-Sanchez R, Pons-Llanas O, Candela-Juan C, *et al*. Two years results of electronic brachytherapy for basal cell carcinoma. *J Contemp Brachytherapy* 2017;9:251–255.
[44] Ballester-Sanchez R, Pons-Llanas O, Candela-Juan C, *et al*. Efficacy and safety of electronic brachytherapy for superficial and nodular basal cell carcinoma. *J Contemp Brachytherapy* 2015;7:231–238.
[45] Doggett S, Willoughby M, Willoughby C, *et al*. Incorporation of electronic brachytherapy for skin cancer into a community dermatology practice. *J Clin Aesthet Dermatol* 2015;8:28–32.
[46] Bhatnagar A, Patel R, Werschler WP, *et al*. High-dose rate electronic brachytherapy: A nonsurgical treatment alternative for nonmelanoma skin cancer. *J Clin Aesthet Dermatol* 2016;9:16–22.
[47] Patel R, Strimling R, Doggett S, *et al*. Comparison of electronic brachytherapy and Mohs micrographic surgery for the treatment of early-stage non-melanoma skin cancer: a matched pair cohort study. *J Contemp Brachytherapy* 2017;9:338–344.
[48] Linos E, VanBeek M, Resneck JS Jr. A sudden and concerning increase in the use of electronic brachytherapy for skin cancer. *JAMA Dermatol* 2015;151:699–700.
[49] Ouhib Z, Kasper M, Perez Calatayud J, *et al*. Aspects of dosimetry and clinical practice of skin brachytherapy: The American Brachytherapy Society working group report. *Brachytherapy* 2015;14:840–858.
[50] Ballester-Sanchez R, Pons-Llanas O, Llavador-Ros M, *et al*. Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology. *J Contemp Brachytherapy* 2015;6:356–361.
[51] Goyal U, Pan J, Cui H, *et al*. Does ultrasound measurement improve the accuracy of electronic brachytherapy in the treatment of superficial non-melanomatous skin cancer? *J Contemp Brachytherapy* 2017;9:14–19.
[52] Guinot JL, Rembielak A, Perez-Calatayud J, *et al*. GEC-ESTRO ACROP recommendations in skin brachytherapy. *Radiother Oncol* 2018;126:377–385.
[53] Hamilton JR, Parvataneni R, Stuart SE, *et al*. Rerecurrence 5 years after treatment of recurrent cutaneous basal cell and squamous cell carcinoma. *JAMA Dermatol* 2013;149:616–618.
[54] Haffty BG, Beyer DC, Kavanagh BD. Radiation oncologist concerns about increased electronic brachytherapy use for skin cancer. *JAMA Dermatol United States* 2015;151:1036.
[55] Goyal U, Kim Y, Tiwari HA, *et al*. A pilot study of ultrasound-guided electronic brachytherapy for skin cancer. *J Contemp Brachytherapy* 2015;7:374–380.
[56] Small W Jr, Beriwal S, Demanes DJ, *et al*. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy* 2012;11:58–67.
[57] Viswanathan AN, Thomadsen B. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles. *Brachytherapy* 2012;11:33–46.
[58] Mobit PN, Nguyen A, Packianathan S, *et al*. Dosimetric comparison of brachytherapy sources for high-dose-rate treatment of endometrial cancer: (192)Ir, (60)Co and an electronic brachytherapy source. *Br J Radiol* 2016;89:20150449.
[59] Kamrava M, Chung MP, Demarco J, *et al*. Electronic brachytherapy for postsurgical adjuvant vaginal cuff irradiation therapy in endometrial and cervical cancer: a retrospective study. *Brachytherapy* 2013;12:141–147.
[60] Dickler A, Puthawala MY, Thropay JP, *et al*. Prospective multicenter trial utilizing electronic brachytherapy for the treatment of endometrial cancer. *Radiat Oncol* 2010;5:67.
[61] Dooley WC, Thropay JP, Schreiber GJ, *et al*. Use of electronic brachytherapy to deliver postsurgical adjuvant radiation therapy for endometrial cancer: A retrospective multicenter study. *Onco Targets Ther* 2010;3:197–203.