Brachytherapy: An Overview for Clinicians

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Abstract: Brachytherapy is a specific form of radiotherapy consisting of the precise placement of radioactive sources directly into or next to the tumor. This technique is indicated for patients affected by various types of cancers. It is an optimal tool for delivering very high doses to the tumor focaly while minimizing the probability of normal tissue complications. Physicians from a wide range of specialties may be involved in either the referral to or the placement of brachytherapy. Many patients require brachytherapy as either primary treatment or as part of their oncologic care. On the basis of high-level evidence from randomized controlled trials, brachytherapy is mainly indicated: 1) as standard in combination with chemoradiation in patients with locally advanced cervical cancer; 2) in surgically treated patients with uterine endometrial cancer for decreasing the risk of vaginal vault recurrence; 3) in patients with high-risk prostate cancer to perform dose escalation and improve progression-free survival; and 4) in patients with breast cancer as adjuvant, accelerated partial breast irradiation or to boost the tumor bed. In this review, the authors discuss the clinical relevance of brachytherapy with a focus on indications, levels of evidence, and results in the overall context of radiation use for patients with cancer.

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Introduction

Brachytherapy is a specific form of radiation therapy used to treat cancer. It consists of placing sealed, radioactive sources directly into or next to the tumor to be treated, either directly or by means of catheters. Brachytherapy has been a part of anticancer treatments since the development of contact brachytherapy in the early 1900s. A few years after the discovery of radioactivity, Pierre Curie and Alexander Graham Bell independently observed shrinkage of malignant tumors when radioactive sources were implanted directly inside a mass.1 Throughout the mid-20th century, brachytherapy use continuously increased, and the technique has become the standard of care as a single modality or as a boost after external-beam radiotherapy (EBRT) for tumors requiring a high radiation dose to be cured.2,7

In 2019, brachytherapy remains an optimal tool in the context of radiation use for patients and may involve a wide range of medical specialties in either the referral to or the placement of brachytherapy. In this review, the clinical relevance of brachytherapy in the global oncological landscape is examined in the light of potential gains in local control, survival, quality of life (QOL), treatment sequelae, and value-based evaluations.

Brachytherapy in the Context of Radiation Use for Patients

Treatment Modalities

Schematically, radiation therapy is indicated in 3 major situations: 1) as curative, definitive radiotherapy (with or without chemotherapy); 2) as adjuvant treatment...
to decrease the probability of local relapse after surgery; and 3) as palliative treatment of symptomatic metastases. The common objective of all irradiation techniques is to deliver a radiation dose to the tumor that is high enough to eradicate tumor cells without leading to unacceptable damage to normal tissues. The deoxyribonucleic acid (DNA) chain is the primary target of therapeutic irradiation, and, if not repaired, radiation-induced DNA damage leads to direct cell death, cell cycle redistribution, and microenvironment changes. The therapeutic index of irradiation relies on the differential response between tumors and normal tissue, as tumors cells have a lower DNA repair capability compared with normal tissue cells. However, radiation-induced changes in organs at risk may lead to acute side effects and long-term functional sequelae. Therefore, the ideal technique should be able to deliver therapeutic doses to the tumor with doses as low as possible to the organs at risk.8

Schematically, 2 possibilities do exist for delivering therapeutic irradiation: EBRT and brachytherapy. In EBRT techniques, which are the most commonly used, the irradiation comes from beams generated outside the patient. Modern EBRT modalities include intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy, and proton therapy. All of those techniques have been developed to increase the ratio between tumor dose and normal tissue dose. The fundamental specificity of brachytherapy is that it relies on the implantation of radioactive sources (or catheters secondarily loaded with radioactive sources) within the tumor (interstitial brachytherapy) or very close to the tumor (plesiotherapy). The implantation is guided by clinical findings and any relevant imaging modality. In some situations, the precise perioperative placement of brachytherapy catheters may need expertise from organ specialists, including urologists, gynecologic surgeons, cardiologists, gastroenterologists, pneumologists, surgical oncologists, interventional radiologists, orthopedists, or dermatologists. This multidisciplinary approach is particularly required for perioperative procedures, in case the target volume is not easily accessible without endoscopic guidance (eg, esophageal or endobronchial tumors) or is close to highly sensitive organs. Thereafter, imaging is done during or just after implantation to guide the dosimetric process, which schematically consists in deciding where the sources should be placed and/or how long those sources should stay in place to achieve a high dose to the tumor without exceeding organs-at-risk dose constraints. The total dose can be delivered through 1) continuous low-dose-rate (LDR) irradiation, 2) low-intensity pulses repeated every hour for up to a few days (pulse-dose-rate irradiation), or 3) a few fractions delivering high doses each time (high-dose-rate [HDR] irradiation). Various radioisotopes with specific properties in terms of half-life and energy can be used; the most commonly used in modern brachytherapy are iridium-192, cobalt-60, iodine-125, and palladium-103.

Advantages of the Technique

The efficacy of brachytherapy relies on the very high radiation dose delivered directly to the tumor, close to the sources. A specificity of brachytherapy is that there is a rapid dose fall-off at distance from the sources, limiting dose exposure of surrounding tissues. Brachytherapy offers dosimetric advantages with very sharp radiation dose gradients compared with conventional external-beam techniques. Furthermore, there is no need for additional uncertainty margins around the clinical target volume. Indeed, if the tumor moves during the irradiation procedure, the radiation source moves as well. This property differs from conventional EBRT, which requires additional margins to consider set-up and organ motion uncertainties.9 Therefore, brachytherapy combines optimal tumor-to-normal tissue gradients while minimizing the integral dose to the rest of the patient. Treatment can be delivered within a few days compared with protracted fractionated radiotherapy schemes, and this is clinically relevant in proliferating tumors to decrease the overall treatment time, thereby improving local control by limiting tumor repopulation.9 Dosimetric studies have confirmed that brachytherapy was an optimal tool in the context of radiation use to achieve high tumor doses while decreasing the dose to organs at risk.10-12 Brachytherapy can be used either alone or in combination with EBRT to increase the dose focally in advanced primary tumors requiring high doses to be cured, such as cervical cancer or prostate cancer (PCa).13

Figure 1 illustrates the specificity of brachytherapy in terms of dose distribution. As very high doses are delivered, acute reactions (inflammation and irritation at the treatment site) are frequent and may be minor to intense, depending on the dose, the site, and the volume treated. As for other invasive treatments, there is a risk of infection and perioperative pain. However, there is a significant decrease in the irradiated volume, and this contributes to the good long-term functional outcome of brachytherapy, with the potential for less global normal tissue fibrosis (which is one underlying mechanisms of organ dysfunction) than with external radiotherapy. This is relevant to decrease long-term morbidity in some clinical situations, such as head and neck cancers, anal canal cancer, or breast cancer.

Constraints

The main limitation of interstitial brachytherapy is that it is invasive, requiring a short procedure in the operating room to place the sources or the catheters. Another key point of brachytherapy is that the quality of implantation is an important parameter of the therapeutic index. Indeed, any inappropriate positioning of the sources may expose the
tumor to underdosage or excessive toxicity if the sources are too close a critical organ. The importance of individual expertise and the implementation of a specific brachytherapy workflow must be appraised. A learning period does exist, especially for sophisticated brachytherapy treatments, and a correlation between increased experience, ability to fulfill planning aims, and clinical outcome has been demonstrated. The possibility that the outcome after brachytherapy is affected by the skills of the center and the activity of the clinician (as for surgical procedures), as is frequently observed in oncological practice, should be considered but should not prevent the center from performing brachytherapy. Given the logistical issues inherent to brachytherapy and the high level of expertise required for implantation, there is an increasing temptation to propose alternative techniques that are easier to implement. The increasing gap between high-tech EBRT and brachytherapy in terms of physician reimbursement may also contribute to adding potential financial disincentives against brachytherapy delivery.

**Improving the Therapeutic Index Through Brachytherapy: The Cervical Cancer Example**

**Level of Evidence**

In international guidelines, the standard treatment for patients with locally advanced cervical cancer (LACC) relies on external radiotherapy combined with concurrent chemotheraphy, followed by a brachytherapy application to increase focally the dose to the primary tumor. Other approaches, including neoadjuvant chemotherapy and radical surgery, were found to be inferior to concomitant chemoradiation plus brachytherapy in a randomized phase 3 study. In that study, the 5-year disease-free survival rate was 69.3% in the neoadjuvant chemotherapy plus surgery group compared with 76.7% in the concomitant chemoradiation plus brachytherapy group (hazard ratio, 1.38; P = .038). Furthermore, 45% of the patients treated with neoadjuvant chemotherapy needed postoperative radiotherapy because of poor prognostic factors for locoregional relapse. Another trial from the European Organization for Research and Treatment of Cancer compared both approaches, and the study definitive results are pending. Preliminary toxicity data show that short term severe adverse events occurred more frequently in the neoadjuvant chemoradiotherapy plus surgery group, mainly related to systemic treatments.

**Practical Aspects**

Brachytherapy application consists of inserting a plastic tube within the uterine cavity and an applicator within the vaginal cavity. This insertion may be done under general or spinal anesthesia, as it requires dilatation of the cervical canal. The development of modern applicators has facilitated the implantation of needles to treat distal tumor extensions within the parametrium. After implantation, non-permanent sources are placed automatically within the applicator according to a personalized treatment plan. Historically, brachytherapy was based on radiographs (2-dimensional), and only marginal personalization of the dose distribution was possible. The implementation of computed tomography or magnetic resonance imaging (MRI) for 3-dimensional treatment planning has enabled one to accurately tailor treatments to patients and their specific tumors. An example of the successive steps in the brachytherapy procedure is shown in Figure 2. Guidelines have been written to homogenize treatment delivery, and new concepts integrating tumor regression during treatment have been implemented. The therapeutic index in patients with LACC who receive brachytherapy has progressively increased after a step-by-step process to refine treatment quality (Fig. 3). A randomized controlled trial comparing modern image-guided brachytherapy versus conventional radiograph-based brachytherapy in LACC is accruing.
Although such a study design raises ethical issues and may be anachronistic, validation of a new technology through a prospective randomized study is imperative.

Results

The refinement in brachytherapy technology optimization capabilities has allowed the delivery of doses >85 to 90 Gray (Gy) in advanced tumors to achieve a local control probability of >90%.

At the same time, doses to the organs at risk (rectum, bladder, sigmoid, bowel) have been significantly decreased, and it is now possible to keep the absolute probability of severe rectal, bladder, or small bowel complications below 5%.

Despite the significant decrease in severe urinary and gastrointestinal morbidities with modern brachytherapy, the long-term effects of the whole therapeutic sequence (chemoradiation plus brachytherapy) remain an issue that needs to be addressed in a multidisciplinary setting, involving gynecologists, psychologists, and sexologists. Those symptoms mainly include menopause and definitive sterility, as well as vaginal sequelae. Indeed, the ovaries, uterus, and potentially involved parts of the vagina are considered as part of the target volumes to be irradiated by EBRT because of a risk of tumor cell dissemination. Ongoing studies are examining how to minimize the risk of vaginal stenosis, dyspareunia, and QOL impairment. The use of vaginal dilators and/or hormone replacement therapy usually is proposed after treatment to prevent or treat symptoms.

Compliance to Standards

Despite the very good results obtained with modern brachytherapy, there has been a trend toward using modern external irradiation facilities to replace brachytherapy, and this trend has been associated with an increased risk of local relapse and poorer cause-specific survival.

An analysis from the National Cancer Data Base showed that brachytherapy use for LACC decreased from 96.7% in 2004 to 86.1% in 2011. Cancer-specific survival was significantly poorer among women who did not receive brachytherapy after controlling for other prognostic factors. The decrease in the use of brachytherapy was most prominent in lower volume treatment centers. In large analyses from US databases including thousands of patients, it was shown that less than one-half of patients treated for LACC received treatment that met all 3 quality benchmarks: overall treatment time (which is an independent prognostic factor for local control), brachytherapy use, and concurrent chemotherapy.

Factors associated with a higher probability of receiving standard-of-care treatment were high-volume centers, academic centers, comprehensive community cancer centers, private insurance, and higher income. Overall survival (OS) was superior in patients treated with brachytherapy (hazard ratio, 0.554; \( P < .001 \)). These data point out that significant disparities in access to standard-of-care treatments (including brachytherapy) have a significant impact on the probability of a cure, although the impact of both known and unknown confounding factors cannot be entirely ruled out. A close
Brachytherapy in the Global Oncological Landscape

**Major Implications**

Apart from cervical cancer, major indications for brachytherapy are endometrial, prostate, and breast cancer (Table 1). For these tumor sites, the level of evidence for brachytherapy has come from randomized controlled studies[4-6,14,25,28-47] focusing not only on local control but also including OS and QOL analysis (Table 2).[4-6,16,25,30,32-42,47-52]

**Endometrial cancer**

Postoperative brachytherapy for endometrial cancer consists of the placement of an applicator within the vaginal cavity to irradiate very focally the vaginal vault and the upper 2 to 3 cm of the vaginal cavity to a depth of 5 mm. This treatment is usually conducted through 3 to 4 fractions given on an outpatient basis. The objective is to potentially sterilize residual cells in the vaginal vault and to avoid a vaginal recurrence. Because the irradiated volume is very small and the total dose is relatively low, this treatment is usually very well tolerated with only minor and transient acute side effects (proctitis, cystitis, vaginal discharge).

The tolerance profile of brachytherapy is clearly superior to that of adjuvant pelvic EBRT, which involves large volumes of the bowel and bladder. The place of brachytherapy in surgically treated patients has been well documented in endometrial cancer through well-conducted clinical trials designed to develop alternatives to radiotherapy to decrease morbidity. In the case of intermediate-risk endometrial cancer, 2 randomized studies have examined the possibility of replacing postoperative EBRT with vaginal vault brachytherapy only.[39,40] EBRT decreased pelvic recurrences compared with vaginal vault brachytherapy alone but yielded no survival benefit and impaired QOL and global health status. The detrimental effect of EBRT was mainly a consequence of bowel morbidity.[40,43] These randomized studies have refined postoperative treatments. In patients with intermediate-risk endometrial cancer (stage I and grade 1-2 according to the International Federation of Gynecology and Obstetrics, \( \geq 50\% \) myometrial invasion, no lymphovascular involvement), postoperative vaginal vault brachytherapy is now recommended to decrease vaginal recurrence with low morbidity. In case of unfavorable factors (eg, lymphovascular involvement and/or the presence of grade 3 disease), recent guidelines now include whether a comprehensive surgical lymph node staging has been performed: if a surgical lymph node staging has been performed and is negative, adjuvant vaginal vault brachytherapy alone is appropriate to spare the bowel morbidity.
TABLE 1. Major Indications for Brachytherapy

| CANCER SITES | INDICATIONS AND QUALIFICATION CRITERIA (ACCORDING TO NCCN 2019) |
|--------------|------------------------------------------------------------------|
| Cervix       | Intact uterus: locally advanced, standard as boost modality; early stage, boost after EBRT in medically inoperable patients |
|              | Postoperative: combined with EBRT in case of positive margins |
| Endometrium  | Adjuvant treatment in surgically staged patients: to be considered or strongly suggested (depending on the number of risk factors) in FIGO stage IA, grade 1-2 in case of risk factors (age ≥ 60 years and/or LVI); recommended in stage IA grade 3 and stage IB grade 1-2; recommended in stage II grade 1-2 (± EBRT); indicated in combination with EBRT for boosting vaginal vault in HR patients (FIGO stage IB, grade 3) or in advanced disease |
|              | Patients not amenable to surgery: boost modality in combination with EBRT |
| Prostate     | Sole therapy (LDR): therapeutic option: 1) very LR patients with expected survival ≥20 y (T1c, GS ≤6, PSA <10 ng/mL, <3 biopsies positive, ≤50% cancer in each fragment/core, PSA density <0.15 ng/mL/g); 2) LR patients with expected survival ≥10 y (T1-T2a, GS ≤6, PSA <10 ng/mL); 3) favorable IR patients (1 IR factor [T2b-T2c OR GS 3 + 4 = 7 OR PSA 10-20 ng/mL] AND percentage of positive cores ≤50%) |
|              | Prostate boosting (HDR or LDR) after EBRT: 1) unfavorable IR group (2 or 3 IR factors: T2b-T2c OR GS 3 + 4 = 7 OR PSA 10-20 ng/mL, AND/OR one of the following factors: GS 4 + 3, percentage of positive cores ≥50%; 2) HR group with expected survival ≥5 y or symptomatic (T3a OR GS 5 OR GS 4 + 5 = 9 OR PSA > 20 ng/mL); 3) very HR group with expected survival ≥5 y or symptomatic (T3b-T4 OR primary Gleason pattern 5 OR > 4 cores with GS 8-10) |
| Breast       | Adjuvant APBI: 1) patients aged ≥50 y with IDC measuring ≤2 cm, with negative margin widths ≥2 mm, no LVI, ER positive, BRCA negative; 2) patients with low-intermediate nuclear grade screening–detected DCIS ≤2.5 cm with negative margin widths ≥3 mm |
|              | Boost to the tumor bed after whole-breast irradiation in case of factors of local relapse after BCS |

Abbreviations: ±, with or without; ADT, androgen deprivation therapy; APBI, accelerated partial breast irradiation; BCS, breast-conserving surgery; BRCA, breast cancer susceptibility genes; DCIS, ductal carcinoma in situ; EBRT, external-beam radiotherapy; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics (version 2009); GS, Gleason score; HDR, high-dose-rate; HR, high-risk; IDC, invasive ductal carcinoma; IR, intermediate-risk; LDR, low-dose-rate; LVI, lymphovascular invasion; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.

associated with EBRT. Otherwise, pelvic EBRT may be still indicated to decrease locoregional recurrence.33,44 Vaginal vault brachytherapy is also indicated in more advanced stages (eg, in case of cervical or parametrical involvement or high-grade disease) to decrease local failure in combination with EBRT (with or without chemotherapy). Therefore, the modern management of endometrial cancers is tailored to each specific situation and is part of a multimodal approach aimed at decreasing morbidity without jeopardizing the probability of survival. The phase 3 Postoperative Radiation Therapy in Endometrial Carcinoma 4 (PORTEC-4) study evaluates the possibility of guiding adjuvant treatments in high-intermediate risk endometrial cancer based on a molecular-integrated risk profile.45 Thus, regarding endometrial cancer treatment, a close collaboration is required with gynecological oncologists to move from a standard approach to risk-adapted strategies.

Breast cancer

Accelerated partial breast irradiation (APBI) is an attractive adjuvant approach in selected patients with breast cancer. It is performed as perioperative or postoperative treatment and consists of placing nonpermanent sources within the tumor bed to decrease the risk of local relapse by delivering focused irradiation to treat only the lumpectomy bed plus a safety margin after breast-conserving surgery (BCS). Compared with whole-breast irradiation, it shortens the 5-week to 7-week course of conventional irradiation and avoids irradiation of the surrounding normal breast tissue, skin, lung, and heart. Conflicting results regarding the safety of APBI have been published from studies using different techniques (including intraoperative radiotherapy and 3-dimensional conformal radiotherapy, with disappointing cosmetic results and more frequent ipsilateral recurrences).46,47,52 In contrast to APBI data based on external radiotherapy techniques, one randomized noninferiority trial compared brachytherapy-based APBI versus whole-breast irradiation for patients with early stage, low-risk breast cancer after BCS and showed the noninferiority of adjuvant brachytherapy with respect to 5-year local control, disease-free survival, and OS.7 Late toxicity profiles and cosmetic results were similar, with significantly fewer grade 2 and 3 late skin side effects after APBI with interstitial brachytherapy, and QOL was not worse with APBI.53,54 That study supports the routine use of interstitial, multicatheter, brachytherapy-based APBI in the treatment of patients with low-risk breast cancer according to study criteria who undergo BCS with free resection margins and without lymphovascular involvement. The decrease in late skin toxicities is relevant, in addition to the improved convenience of treatment delivery. A cost analysis compared whole-breast irradiation with 2 APBI techniques for early breast cancer and showed that whole-breast irradiation was the least costly technique to the health care system, but APBI techniques were less costly to the patients.54 One major aspect of brachytherapy for APBI strategies is that they require close collaboration with surgeons to ensure that the initial tumor location is properly irradiated. Furthermore, not all patients are good candidates and, apart from the histopathological features mentioned in Table 1 the distance to the skin (to avoid telangiectasia due to high-dose sleeves close to the sources),
### TABLE 2. Major Randomized Phase 3 Studies Assessing the Place of Brachytherapy in Cancer Therapeutic Strategies (Trials Comparing Various Fractionation Schemes Were Not Included)

| INDICATION                                      | NO.  | TREATMENT MODALITY                                      | RESULTS                                                                                                           | REFERENCES                                                                 |
|------------------------------------------------|------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Supratentorial malignant astrocytoma             | 140  | EBRT at 50 Gy in 25 fractions + temporary stereotactic \(^{125}\) \(_{I}\) implants (minimum peripheral tumor dose of 60 Gy) | Median survival was 13.8 mo after BT vs 13.2 mo (\(P = .49\))                                                   | Laperriere 1998\(^{15}\)                                                  |
| Locally advanced NPC (IAEA trial)               | 247  | Induction CT, followed by CRT + BT boost               | No benefit in 3-y local recurrence-free survival; no increase in grade 3-4 toxicity                              | Rosenblatt 2010\(^{31}\)                                                  |
| Uveal melanoma (COMS trial)                     | 1317 | \(^{125}\) \(_{I}\) BT vs enucleation               | No survival difference between enucleation and BT                                                               | COMS 2006\(^{36}\)                                                       |
| Soft-tissue sarcoma treated with complete resection | 164  | Adjuvant BT (\(^{192}\) \(_{Ir}\) implant, delivering 42-45 Gy over 4-6 d) vs no further therapy | 5-y actuarial LC rates: 82% vs 69% in favor of BT (\(P = .04\)); no impact on LC in patients with low-grade lesions; no impact on metastasis or CSS | Pisters 1996\(^{57}\)                                                   |
| LR prostate cancer                              | 165  | Robot-assisted radical prostatectomy vs BT             | No difference in bRFS; significantly higher IPSS scores and continece rates in BT arm during the first 6 mo (\(P < .05\) for both) but lower potency rates (\(P < .05\)) | Schlussel 2018\(^{48}\)                                                  |
| Prostate carcinoma stage T1-T3, PSA <50 ng/mL (93% intermediate-high risk) | 216  | EBRT delivering 55 Gy in 20 fractions vs EBRT followed by HDR BT (2 × 8.5 Gy) | BT boost improved biochemical/clinical RFS (31% reduction in the risk of recurrence; \(P = .01\)); severe late urinary and rectal morbidity similar | Hoskin 2012\(^{4}\)                                                      |
| Intermediate-risk and high-risk prostate cancer (ASCENDE-RT trial) | 398  | 12 mo of ADT, pelvic EBRT (46 Gy), followed by EBRT boost to 78 Gy vs LDR prostate BT boost | 7-y bRFS in favor of BT boost (86% vs 75%; \(P < .001\)); acute and late GU morbidity higher after LDR boost; no differences in erectile dysfunction | Morris 2017\(^{6}\)                                                      |
| cT2-cT3, surgically staged, lymph node–negative prostate cancer | 104  | EBRT (40 Gy/20 fractions) with iodine implant (35 Gy) vs EBRT alone (66 Gy/33 fractions) | Biochemical control was improved by a BT boost (HR, 0.53; 95% CI, 0.31-0.88); no difference in OS, CSS, or metastatic events | Days 2017\(^{5}\)                                                      |
| LR IDC and ductal carcinoma in situ treated with BCS (GEC-ESTRO trial) | 1184 | WBRT vs interstitial multicatheter APBI | No difference in local recurrence; 5-y grade 2-3 late skin effects: 3.2% with APBI vs 5.7% with EBRT (\(P = .08\)); better symptom scores after APBI at 3 mo | Polgar 2017\(^{51}\)                                                      |
| Breast IDC T1-T2 ≤3.5 cm, N0-N1 invasive, age ≥45 y (TARGIT-A trial) | 3451 | WBRT vs IORT (± whole-breast EBRT according to final pathology) | Recurrence rate was 3.3% after IORT compared with 1.3% after EBRT (\(P = .042\)); grade 3-4 skin complications were significantly reduced with TARGIT | Vaidya 2014\(^{47}\)                                                      |
| Early-stage BC (ELIOT trial)                    | 1305 | After BCS, WBRT vs IORT                                | More frequent 5-y ipsilateral breast recurrences after IORT (4.1% vs 4% [HR, 9.3; 95% CI, 3.3-26.3]); no difference in OS; fewer skin side effects after IORT (\(P = .0002\)) | Veronesi 2013\(^{52}\)                                                    |
| LACC stage IB2-IIIB                             | 211  | CRT (50.4 Gy) with CDDP and gemcitabine followed by BT boost or radical hysterectomy + LND | PFS and OS were similar; no difference was observed in the pattern of failures | Cetina 2013\(^{25}\)                                                      |
| LACC stage IB2-IIIB                             | 635  | Neoadjuvant CT (carboplatin/ paclitaxel) followed by radical hysterectomy vs standard CRT + BT | 5-y DFS higher in the standard arm (69.3% vs 76.7%; \(P = .038\)); no impact on 5-y OS | Holschneider 2019\(^{16}\)                                               |
| HIR endometrial stage I-IIIA cancer surgically treated (PORTEC-2) | 427  | Adjuvant EBRT vs VB                                     | No differences in OS or DFS; acute and late grade 1-2 GI toxicity lower in the VB group (12.6% vs 53.8%) | Nout 2010,\(^{40}\) de Boer 2015\(^{41}\)                                   |
| Medium-risk endometrial carcinoma surgically staged (Swedish trial) | 527  | Adjuvant VB vs VB + EBRT                               | 5-y locoregional relapses higher after VBT alone (1.5% vs 3%; \(P = .013\)); no impact on OS; higher GI/GU morbidity after EBRT, with impact on QOL | Sorbe 2012,\(^{39}\) Sorbe \(^{42}\)                                      |
| NSCLC, stages I-IIIB, with endobronchial tumor in the proximal airways | 95   | EBRT + endobronchial BT (2 × 7.5 Gy at 1 cm) | The addition of BT was safe and provided higher rates of re-expansion of a collapsed lung, resulting in a transient lower level of dyspnea | Langendijk 2001\(^{38}\)                                                  |
| Malignant biliary strictures                     | 42   | PCS followed with intraluminal \(^{192}\) \(_{Ir}\) BT and EBRT vs stent insertion only | OS in favor of percutaneous BT: 298 vs 387.9 d (\(P < .05\)) | Valek 2007\(^{32}\)                                                      |
the distance to the ribs (to avoid extremely rare cases of weakness and fracture of the ribs), and the patient’s anatomy should be considered.

**Prostate cancer**

LDR brachytherapy, consisting of placing permanent radioactive iodine-125 seeds into the prostate (or, less frequently, palladium-103 seeds), is indicated as monotherapy in patients with low-risk PCa who require or choose active treatment. LDR brachytherapy is considered as an option for patients who have favorable intermediate-risk disease (Gleason 7, prostate-specific antigen <10 ng/mL; or Gleason 6, prostate-specific antigen 10-20 ng/mL). The technique has several advantages over other options: compared with radical prostatectomy, it is a simple and minimally invasive technique that can be performed as an outpatient procedure under spinal anesthesia with rapid recovery and a lower incidence of dribbling. Prostate HDR brachytherapy can be also performed over a few sessions consisting of inserting catheters within the gland using high-activity radioactive sources of iridium-192. This technique is mainly used as a boost to the prostate in combination with EBRT, but monotherapy is safe and effective as well. Compared with EBRT, brachytherapy allows for increasing the radiation to a dose much greater than what can be delivered by more sophisticated EBRT techniques. In fact, there is a large amount of evidence that increasing the dose to the prostate is associated with an improvement in biochemical progression-free survival in PCa. On the basis of accumulating evidence from nonrandomized studies and from one single randomized comparison that included a few patients, permanent seed brachytherapy as monotherapy is equivalent to radical prostatectomy in patients who have low-risk PCa, with less urinary incontinence and/or erectile dysfunction in the short term.

A feasibility study has shown that recruitment to surgery versus brachytherapy is not feasible using 2-step randomization, illustrating the difficulty of comparing both strategies. In addition to tumor-related qualification criteria, the estimated life expectancy, prostate volume (<5 cm³), and preexisting urinary symptoms must be taken into account to guide treatment and maximize the therapeutic index. In case of significant urinary symptoms, surgery may be preferred.

Three randomized studies have tested dose escalation through a brachytherapy boost for patients with intermediate-risk and high-risk PCa using various total doses, various fractionations, and various androgen deprivation therapy (ADT) approaches. The addition of brachytherapy to EBRT drastically reduced the biochemical recurrence rate but, to date, without improving OS, cause-specific survival, or metastasis-free survival. The largest trial, the ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) study, enrolled 398 patients with intermediate-risk and high-risk cancer who were randomized to either a standard arm, which included 12 months of ADT and pelvic irradiation to 46 Gy followed by a dose-escalated EBRT boost to 78 Gy, or an experimental arm, with a boost to the prostate gland through permanent prostate implants. That trial showed that the probability of biochemical failure at a median follow-up of 6.5 years was twice as high among patients who received an EBRT boost compared with those who received a brachytherapy boost. Regarding toxicity, 2 trials using an HDR brachytherapy boost reported equivalent urinary toxicity, bowel morbidity, and QOL. In the ASCENDE-RT trial, there was no difference in the frequency of erectile dysfunction, but a higher incidence of acute and late genitourinary morbidity was reported after brachytherapy, suggesting that appropriate patient selection based on preexisting urinary function is warranted, especially if permanent prostate implants are used. A large retrospective cohort study of patients with Gleason 9 and 10 disease has suggested the superiority of EBRT followed by a brachytherapy boost with ADT in terms of cancer-specific mortality and time to distant metastasis.

### TABLE 2. Continued

| INDICATION                                          | NO. | TREATMENT MODALITY | RESULTS                                                                 | REFERENCES |
|-----------------------------------------------------|-----|--------------------|------------------------------------------------------------------------|------------|
| Palliative treatment of inoperable patients with thoracic esophageal SCC (IAEA trial) | 232 | HDR-BT + EBRT vs HDR-BT alone | Dysphagia relief, symptoms were improved with combined therapy at 200 d from randomization (P = .019) | Rosenblatt 201033 |
| Esophageal SCC                                       | 103 | EBRT ± BT boost    | No difference in 5-y CSS (27% vs 38%); CSS was improved in the BT group among patients with tumor length ≤5 cm | Okawa 199934 |

Abbreviations: ±, with or without; ADT, androgen deprivation therapy; APBI, accelerated partial breast irradiation; ASCENDE-RT trial, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial; BC, breast cancer; BCS, breast-conserving surgery; BT, brachytherapy; brachytherapy; BRFS, biochemical relapse-free survival; CDDP, cisplatin; COMS, Collaborative Ocular Melanoma Study; CRT, chemoradiation; CSS, cause-specific survival; CT, chemotherapy; DFS, disease-free survival; EBRT, external-beam radiotherapy; GEC-ESTRO trial; European Curie Therapy Group-European Society for Radiotherapy and Oncology trial; GI, gastrointestinal; GU, genitourinary; Gy, grays; HDR, high-dose-rate; HIR, high-intermediate risk; HR, hazard ratio; IAEA, International Atomic Energy Agency; ELIOT trial, Intraoperative Radiotherapy With Electrons trial; I125, iodine-125; IDC, intraductal carcinoma; 192Ir, iridium-192; IORT, intraoperative radiotherapy; IPSS, International Prostate Symptom Score; LACC, locally advanced cervical cancer; LC, local control; LDR, low-dose-rate; LND, lymph node dissection; LR, low-risk; NPC, nasopharyngeal carcinoma; NSCLC, non–small cell lung cancer; OS, overall survival; PCa, prostate cancer; PCS, percutaneous stent; PFS, progression-free survival; PORTEC trial, Post-Operative Radiation Therapy in Endometrial Carcinoma trial; PSA, prostate-specific antigen; QOL, quality of life; SGC, squamous cell carcinoma; TARGIT, Targeted Intra-Operative Radiotherapy; VBT, vaginal brachytherapy; WBRT, whole-breast radiotherapy.
to the last update of American Society of Clinical Oncology/Cancer Care Ontario joint guidelines, a brachytherapy boost should be offered to eligible patients. The number of centers using HDR brachytherapy has increased in recent years, whereas there has been a declining use of brachytherapy alone for low-risk patients compared with more costly therapies, including robotic surgery, IMRT, proton therapy, or stereotactic body radiotherapy. Recent analyses have shown that brachytherapy boosts for PCa lowered the expected lifetime treatment costs because of a decrease in the incidence of metastatic castration-resistant PCa, thus avoiding the use of expensive systemic targeted treatments. Prostate brachytherapy boosts are statistically less costly to Medicare and the institution than IMRT boosts \((P < .001)\), and seeds are less costly than HDR brachytherapy \((P = .01\) and \(P < .001\), respectively). Patients need to be involved in making treatment decisions. When surgery, external radiotherapy, and brachytherapy are deemed appropriate therapeutic options, a dedicated brachytherapy consultation is recommended to ensure that patients receive appropriate information. It is particularly important to involve urologists because they refer patients and, in some circumstances, even participate directly in the placement of seeds into the prostate. Furthermore, their expertise may be required for the treatment of genitourinary complications. After brachytherapy implantation, acute complications include a change in the International Prostate Symptom Score and urinary retention. Chronic side effects mainly include permanent urinary symptoms and erectile dysfunction. Radiation proctitis may occur, sometimes requiring a laser to treat rectal telangiectasia. These side effects must be weighed against those of other treatment options: incontinence and erectile dysfunction (for surgery) and bowel symptoms (for EBRT). In a large analysis of patient-reported QOL among men with localized PCa, it was shown that, compared with active surveillance, worsened urinary incontinence was associated with radical prostatectomy, acute worsening of urinary obstruction and irritation were associated with EBRT and brachytherapy, and worsened bowel symptoms were associated with EBRT (symptom score, 4.9; 95% CI, 2.4–7.4). In most domains, mean scores did not differ between active surveillance and treatment at 24 months.

Organ-Sparing Multimodal Strategies

Brachytherapy is appropriate as monotherapy to treat small tumors that are accessible for implantation using visual, manual, or radiological guidance (Fig. 4). Its properties make the technique optimal for conservative treatments to avoid mutilating surgery without jeopardizing the probability of a cure. Physicians from a wide range of specialties may be involved in the referral, in the placement of brachytherapy, as well as in the management of treatment sequelae. Selected examples are provided below.

**Penile glans cancer**

Retrospective cohorts have shown that high local control (>80% at 5 years) could be achieved with brachytherapy for selected penile glans carcinomas without infiltration of the corpus cavernosum. Although quite impressive to the patients, this is usually a well-tolerated technique, and acute side effects are mainly represented by mucositis and urethral inflammation. Brachytherapy offers the advantage of organ preservation because the only alternative would be penile partial or total amputation (Fig. 5). This technique is part of a multimodal approach, as a circumcision is required before treatment to facilitate implantation and decrease acute side effects, and a surgical exploration of the groin (sentinel lymph node procedure or lymph node dissection) may be performed in the same operative time to complete radiological staging and address the regional risk. In the largest published cohort of patients, the 5-year estimated probability of local control was 82% (95% CI, 76%–88%) and 75% of local relapses were efficiently salvaged by second-intent surgery. Late morbidities are mainly represented by urethral stenosis requiring dilatations and painful ulcerations, which may require limited surgery in 7% of patients. The estimated probability of preserving the penis in 5-year survivors was 85% (95% CI, 79%–91%). QOL data have shown that approximately two-thirds of patients treated with brachytherapy continued to maintain sexual activity, with an acceptable impact on functional outcome.

**Pediatric rhabdomyosarcoma**

In children, minimizing integral doses is relevant to avoid second cancers and to avoid the effects of radiotherapy on bone structures and growth as well as long-term gastrointestinal sequelae. Second cancers are among the most feared complications after radiotherapy in childhood. Although the specific impact of modern technologies is still under investigation, theoretical models suggest that IMRT may increase the risk of second malignancies as a consequence of the increase in the volume of normal tissues receiving low doses. Therefore, it is very important to keep irradiated volumes as low as possible to minimize the risk of second cancers and, in this context, brachytherapy has been proposed with high efficacy and acceptable morbidity by expert teams in pediatric patients as part of a multimodal conservative strategy for children with bladder and/or prostate rhabdomyosarcoma. This approach, combining open surgery and catheter placement in the same procedure, requires a close collaboration between surgeons and brachytherapists. A strategy combining brachytherapy and an ovarian transposition also has been proposed in young girls with gynecological malignancies and has produced very high local control rates (Fig. 6).

**Anal cancer**

In anal canal carcinoma, brachytherapy may be used for boost delivery after EBRT in selected patients (if less than one-half
of the circumference is involved and there is <5-10 mm residual tumor depth). The purpose is to focally increase the dose while sparing the uninvolved part of the anal canal to minimize sphincter dysfunction. Needles are implanted along the anal canal through a transperineal approach, and fixed with a template at the perineal skin to keep the needles in place during the whole treatment. A retrospective analysis published in 2011 suggested that brachytherapy was the best boost modality in terms of the cumulative rate of local recurrences; however, no confirmatory, prospective study has been conducted, and this technique requires operator experience to properly define the tumor site to be treated. A close collaboration between radiation oncologists, proctologists, and brachytherapists is crucial. Furthermore, not all patients can be treated by brachytherapy, and selection criteria should be followed to avoid (or at least minimize) the risk of necrosis. 

Head and neck cancers

In head and neck cancers (lip, mobile tongue, floor of mouth, basal tongue, soft palate, oral mucosa), brachytherapy is indicated alone or in combination with other treatments (EBRT and/or surgery) depending on the location, tumor size, and lymph node involvement. This is a first-choice radiotherapy technique for sparing salivary function. It is estimated that >90% of all lip cancers are appropriate indications for brachytherapy, offering the best functional and esthetic results with local control rates ranging from >90% to 95%, all stages included (Fig. 7). However, acute reactions are frequently intense and require local applications with or without analgesics for a few weeks. After the acute phase and healing, long-term functional and cosmetic outcomes usually are excellent. Brachytherapy is also indicated as postoperative...
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Tailoring Treatments: Biological and Radiological Insights

Tumor and Blood Biomarkers

The next crucial step in optimization is to personalize treatment objectives to individual patients and tumor characteristics, considering biomarkers that reveal intrinsic radiosensitivity as well as tumor microenvironment physiology to guide treatment delivery. No independently validated, specific blood or tumor biomarker exists for brachytherapy, and most available data have focused on a strategy that may or may not have included brachytherapy. Recent retrospective data have suggested that tumor volumetric reduction after chemoradiation may be used to preferentially guide the optimal boost dose in patients treated for LACC, thus reinforcing the rationale for increasing the dose in poor responding patients. Increasing data suggest that uterine cervical cancers that display tumor-related leukocytosis are a distinct clinical entity with radioresistant features, and such a biomarker may also be used to guide the dose. Predictive biological factors for biochemical recurrence have been proposed in patients with localized PCa who receive brachytherapy, such as positive nuclear staining for DNA-dependent protein kinase, which was associated with a poorer outcome.

The Place of Systemic Treatments

A threshold seems to have been reached in the ability to improve outcomes through dose escalation. In patients who have LACC who are treated with modern brachytherapy, the 5-year local control probability is now reaching 90%, but the outcome still needs to be improved, with 5-year cause-specific survival rates of 73%, all stages included. An analysis of the patterns of relapse showed that most failures are distant, even in patients who achieve...
good local control.\textsuperscript{30} The dismal prognosis of patients with local relapse, for whom salvage surgery efficacy is alleviated by metastatic evolution, suggests that radioresistance and metastases share common biological pathways, one of which is hypoxia.\textsuperscript{81} Therefore, strategies tailored to the metastatic risk (eg, adjuvant chemotherapy) are attractive for combining dose escalation and systemic optimization, reinforced by the finding that ionizing radiation may contribute to inducing metastasis, cancer stem cell phenotype, and oncogenic metabolism in surviving cancer cells.\textsuperscript{82} The example of endometrial carcinoma illustrates the trend to guide brachytherapy indications from molecular-integrated risk profiles.\textsuperscript{45} Immunological perspectives may be opportunities for pharmacological approaches.\textsuperscript{83} Brachytherapy is a very appealing technique to be combined with immunomodulatory drugs and activate anti-tumor immunity. Indeed, brachytherapy properties may be exploited to potentiate immunological interactions: 1) irradiation exposure is very heterogeneous, and tumor cells are exposed to a large range of doses; 2) irradiation of tumor-draining lymph nodes is avoided, which likely is relevant in the context of radioimmunotherapy.

FIGURE 7. Example of Brachytherapy for Lip Cancer Treatment. (A) 70-year old patient with inferior lip squamous cell carcinoma stage T2N0. (B) Implantation was performed with 4 plastic tubes. (C) Prescription isodose (70 Gy) is shown. (D) He presented an intense acute mucositis and was treated with iodine application. 12 weeks. (E) 18 weeks. (F) The patient is in complete response with good cosmetic outcome at 18 months follow-up.

FIGURE 8. Integrating Brachytherapy as Part of a Multimodal Strategy: Example of a Locally Advanced Vulvar Squamous Cell Carcinoma. (A) Primary staging showed a bulky vaginal extension (arrow), as shown on T2-weighted magnetic resonance imaging associated with hypermetabolism on (B) 18-fluorodeoxyglucose positron emission tomography/computed tomography. (C) After 45 Gy of external irradiation delivered through intensity T2-modulated radiotherapy with a concomitant platinum derivate, (D) a good partial response (arrow) was observed, and (E) the patient could receive a brachytherapy boost combining endocavitary and interstitial implantation. (F) Optimal avoidance of the rectum and contralateral vulva and dose escalation to the residual disease could be achieved by dosimetric optimization.
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to potentiate initiation of the antitumor immune response; 3) a low integral body dose minimizes immunosuppression; and 4) biopsies can be performed during the same time as implantation to guide systemic agents and assess histopathological correlations. Therefore, strategies combining brachytherapy with immune checkpoint inhibitors, such as programmed cell death ligand–1 or cytotoxic T-lymphocyte antigen–4 inhibitors, should be encouraged to exploit the immunomodulatory potential of brachytherapy.26

Integrating Modern Imaging
Numerous developments in functional imaging provide opportunities to improve brachytherapy by considering tumor heterogeneity at the macroscopic scale. For example, tumors with an infiltrative shape respond less favorably to chemoradiation than expansive tumors equivalent in size.84 Furthermore, dynamic contrast-enhanced MRI may noninvasively identify an aggressive hypoxic and radioresistant phenotype that is correlated with a hypoxic molecular gene signature.85 Multiparametric MRI based on diffusion, perfusion, and spectroscopic acquisitions, in addition to morphologic assessment, opens perspectives for functional tumor imaging and to guide focal treatments (Fig. 8). This may allow for more accurate volume delineation to test functionally guided dose escalation in cases of resistant tumors or in reirradiation, which is an increasing research area for PCa.86

Conclusions
Brachytherapy is indicated as exclusive treatment or combined with other treatment modalities (external radiotherapy or surgery) in numerous clinical situations, with a high level of evidence that it has a place in the global oncological landscape (Fig. 9). Physicians from a wide range of specialties are involved in the brachytherapy process by referral of patients, in the placement of brachytherapy, and in posttreatment management (follow-up and treatment of complications, if any). Numerous efforts have been made through step-by-step developments to bring brachytherapy to the highest level of modernity and improve the therapeutic index. In the future, brachytherapy should include personalized tools of medical oncology and radiology. Clinical evidence and technological refinements contrast with trends in brachytherapy use.86,87 Health care policies and insurance providers should be encouraged to optimize the organization of patient care to ensure that all patients have the opportunity to receive the standard treatment or can make a choice between available therapeutic options.16 In the context of a global increase in health costs, the perspective of an excellent cost-effectiveness ratio should encourage health care systems to provide guidance in the near future regarding brachytherapy use and requirements for continuing education. Although no robust survival data are available for brachytherapy, potential effects on the probability of achieving a definitive cure suggest that the gains are enormous. ■

FIGURE 9. Brachytherapy Is Indicated in Numerous Clinical Situations Either Alone or Combined With Other Treatment Modalities (External-Beam Radiotherapy or Surgery). High-level evidence indicates that brachytherapy has a place in the global oncological landscape.
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