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The Case for Brachytherapy: Why it deserves a Renaissance

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Abstract:	Given recent global events related to the COronaVIrus Disease-19 (COVID-19) pandemic, the medical landscape and oncologic treatment perspectives have significantly shifted. Oncologic physicians are increasingly focused on maintaining equipoise of treatment outcome and medical accessibility with decreasing medical resource utilization. In support of these measures, radiation oncologists have utilized a variety of temporizing measures including hormone therapy measures (breast, endometrial and prostate cancer), treatment delays (where appropriate), and hypofractionation across all disease sites (1-5). For breast, prostate and gynecologic malignancies, low-dose (LDR) and high-dose rate (HDR) brachytherapy represent the pinnacle of hypofractionated, conformal radiation therapy. Previously, studies showed a decline in both gynecologic (6, 7) and prostate (8) brachytherapy despite data showing superior treatment outcomes. However, newer data suggests that the declining utilization rates may be reversing (9, 10) Brachytherapy treatment approaches are well-tolerated, safe, effective, and cost-effective. As radiation oncologists and patients move forward, brachytherapy represents an often under-utilized and effective treatment modality.

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The Case for Brachytherapy: Why it deserves a Renaissance

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Abstract:

The recent global events related to the COronaVIrus Disease-19 (COVID-19) pandemic have significantly changed the medical landscape and led to a shift in oncologic treatment perspectives. There has been a renewed focus on preserving treatment outcomes while maintaining medical accessibility and decreasing medical resource utilization. Brachytherapy, a vital part of the treatment of many cancers, particularly prostate and gynecologic cancers, has the ability to deliver hypofractionated radiation and thus shorten treatment time. Studies in the early 2000's had demonstrated a decline in brachytherapy usage despite data showing equivalent or even superior treatment outcomes for brachytherapy in disease sites such as the prostate and cervix. However, newer data suggests that this trend may be reversing. The renewed call for shorter radiation courses given data showing that they can provide equivalent outcomes will likely establish hypofractionated radiation as the standard of care across multiple disease sites. With shifting reimbursement, brachytherapy represents the pinnacle in hypofractionated, conformal radiation therapy with extensive long-term data in support of the treatment modality brachytherapy is primed for a renaissance.

Introduction

Given recent global events related to the COronaVIrus Disease-19 (COVID-19) pandemic, the medical landscape and oncologic treatment perspectives have significantly shifted. Oncologic physicians are increasingly focused on maintaining equipoise of treatment outcome and medical accessibility with decreasing medical resource utilization. In support of these measures, radiation oncologists have utilized a variety of temporizing measures including hormone therapy measures (breast, endometrial and prostate cancer), treatment delays (where appropriate), and hypofractionation across all disease sites (1-5). For breast, prostate and gynecologic malignancies, low-dose (LDR) and high-dose rate (HDR) brachytherapy represent the pinnacle of hypofractionated, conformal radiation therapy. Previously, studies showed a decline in both gynecologic (6, 7) and prostate (8) brachytherapy despite data showing

superior treatment outcomes. However, newer data suggests that the declining utilization rates may be reversing (9, 10) Brachytherapy treatment approaches are well-tolerated, safe, effective, and cost-effective. As radiation oncologists and patients move forward, brachytherapy represents an often under-utilized and effective treatment modality.

Gynecologic brachytherapy

Gynecologic brachytherapy is a vital and irreplaceable component of definitive and adjuvant treatment for gynecologic malignancies. Multiple studies have demonstrated the efficacy of brachytherapy to treatment outcomes in cervical and uterine malignancies cancer (11-19). Unfortunately, gynecologic brachytherapy utilization declined paralleled with clinical implementation of intensity- (IMRT) and volumetric-modulated arc therapy (VMAT)(6, 7). Furthermore, attempts to replace brachytherapy with external beam treatment approaches have been unsuccessful. Notably, a recent phase II study in patients with predominantly locally advanced cervical cancer examined the feasibility of using a stereotactic ablative radiotherapy (SABR) boost as an alternative to brachytherapy for medically unfit patients, or those refusing brachytherapy(20). The study was closed early due to high toxicity rates – including death due to complications of therapy. ASTRO cervical cancer clinical practice guidelines state that either SABR or IMRT are only suitable replacements for brachytherapy when considered for patients refusing or ineligible for brachytherapy (21).

Modern high-dose rate (HDR) brachytherapy is a form of hypofractionated, conformal therapy commonly delivered in 4-5 treatments in cervical cancer (22).However, there are two(23) and three(24) fraction regimes that have been utilized more in resource poor setting which can be used to preserve resources in these times . This decreases the treatment time so that curative treatment can be delivered faster. While complex interstitial cases are often done in the OR in the modern era, gynecologic brachytherapy procedures can be safely delivered without utilization of OR time in an HDR suite without the need for anesthesia or through use of moderate sedation for interstitial cases. Advances in imaging

technology such as magnetic resonance imaging (MRI) allows for adaptive image-guided brachytherapy (IGBT) with simultaneous dose escalation to tumor targets and sparing of organs at risk (OAR). Compared with point-based brachytherapy planning, volumetric-based planning using IGBT has demonstrated improved tumor control and significantly reduced toxicity (25-27). Additionally, a cost utility analysis of IGBT showed that MRI has the potential to decrease health care costs compared to two-dimensional or CT-guided guided brachytherapy through reduced costs from cancer recurrence and treatment toxicity (28).

Breast brachytherapy

Partial breast irradiation (PBI) has demonstrated comparable treatment outcomes to whole breast irradiation (WBI) with regard to local tumor control, toxicity, and cosmetic outcomes (29-33). Initially, accelerated partial breast irradiation (APBI) provided a method of shortening typical 5-6 week standard fractionation radiation courses to 5 days. The recent publication of the UK FAST FORWARD study offers an even faster external beam option for the delivery of radiation to the breast (34). However, hypofractionation is still underutilized in the United States(35). Brachytherapy therefore remains a viable, short treatment option with new data exploring non-invasive techniques and even shorter treatment regimens (36, 37).

Early data for breast brachytherapy delivered in 1-4 fractions has demonstrated excellent local tumor control and cosmetic outcomes (37, 38). The phase II Triumph-T trial showed excellent local tumor control (albeit short median follow up) and breast cosmesis using a 3-fraction breast brachytherapy technique, and a similar 4-fraction regimen had excellent cosmesis with no locoregional recurrences at 6 years (37, 39). Furthermore, in elderly patients, single fraction regimens have also demonstrated excellent oncologic outcomes(40), and a recent study comparing PBI to PBI plus endocrine therapy or endocrine therapy alone in women over the age of 70 with low-risk, hormone-

positive early-stage breast cancer demonstrated that PBI was superior when compliance with endocrine therapy was poor(41) and tested compliance interventions have demonstrated no improvement(42, 43). Therefore, even with the likely adoption of shorter external beam radiation treatment regimens, breast brachytherapy remains an excellent option for women and provides good local control and cosmetic outcomes.

Prostate brachytherapy

Prostate brachytherapy results in excellent treatment and toxicity outcomes, has short overall treatment time (OTT), and is more cost-effective than other radiation treatment options. Prostate brachytherapy (HDR or LDR) is considered equivalent to radical prostatectomy and external beam radiation for the treatment of prostate cancer and can be completed in one (LDR) or several implantations (HDR)(44, 45). Use of either LDR or HDR prostate brachytherapy decreases OTT compared to external beam standard fractionation, and some hypofractionation schemes when used as a boost(2). As monotherapy, HDR and LDR approaches have shorter OTT than SABR, which is typically delivered in 5-7 every-other-day fractions(46).

Brachytherapy as monotherapy is appropriate for patients with low-risk or favorable intermediate-risk disease, or as a boost in patients with unfavorable intermediate- and high-risk disease. When used as a boost for patients with unfavorable to high-risk disease, recent data from two prospective randomized trials has shown that brachytherapy significantly prolongs biochemical progression free survival by over 50% compared to dose-escalated external beam radiation (47, 48). Furthermore, retrospective data also suggests that brachytherapy used as monotherapy for low-risk disease can prolong biochemical progression free survival (PFS) compared to either surgery or external beam radiation (45). The median cost of prostate cancer therapy has also been shown to be less with brachytherapy compared with either SABR, IMRT, or proton therapy (49) . A 2013 study by Hayes et al found that brachytherapy was the most effective and least costly initial treatment option for men with

low-risk prostate cancer, including men who chose active surveillance (50). Fortunately though older data had suggested that prostate brachytherapy was declining (51) this trend appears to reversing (10).

Prostate brachytherapy is also useful in the setting of isolated intraprostatic recurrence following definitive treatment with radiation. A recent phase II trial, and several retrospective studies, demonstrated excellent rates of cancer free and biochemical recurrence free survival with brachytherapy and had acceptable, predominantly grade 1 and 2 gastrointestinal and genitourinary toxicity (52-54). Compared to other local salvage techniques such as prostatectomy, high-frequency ultrasound, or cryotherapy, prostate brachytherapy has similar rates of biochemical control at 5 years with lower toxicity rates, such as incontinence and bladder neck stricture(55). Prostate brachytherapy remains an viable treatment option for patients that provides excellent outcomes with acceptable toxicity and is cost effective.

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Economic considerations

The use of hypofractionation in the United States (US) has been increasing leading to declines in radiation oncology departmental revenue through reduced episodic fee-for service (FFS) reimbursement(56, 57). This trend was coincident with a period of transition from volume- to value-based care. During this period the total proportion of US healthcare payments tied to quality- and cost-focused alternative payment models (APMs) increased from 23% in 2015 to 34% in 2017(58). The shift to value-based care was further accentuated by the recent Radiation Oncology Model (RO-APM) proposal from the Centers for Medicare & Medicaid Services (CMS) in 2019(59).

COVID-19 has since accelerated the transition to extreme hypofractionation, including stereotactic radiotherapy and brachytherapy. Following COVID-19, we anticipate the continued use of shorter treatment schedules and modalities that minimize patient exposure to high-cost hospital resources, post-operative care, or hospitalization. Brachytherapy is well-positioned to capitalize on these changes

given its high value proposition. Most brachytherapy treatments can be delivered with minimal resources (2), with lower fully loaded treatment delivery costs via time-driven activity based costing analyses (60, 61), or in alternative locations, such as ambulatory surgery centers or freestanding centers (62). As a low cost modality (63), brachytherapy can be associated with less patient co-insurance and co-payment who may be facing unemployment or reduced income, and loss of health insurance coverage. Despite these benefits, reduced physician reimbursement for brachytherapy has exacerbated revenue declines that have already impacted practices during the pandemic(64). This places radiation oncology practices at further financial risk in an already high fixed-cost business.

Adoption of the RO-APM may improve financial stability by providing episodic payments for disease site-specific radiation oncology care. These payments would be tied to average episode reimbursements rather than the volume or modality of service. This APM re-design appropriately attempts to incentivize shorter courses of low-cost, high-quality treatment (i.e. brachytherapy). This change would also protect physicians from uncontrollable downside risk, such as from COVID-19, and would provide financially stable payments to practices.

However, despite these theoretical benefits, several key changes are necessary to CMS' RO-APM to ensure sustainability of and access to radiation oncology care in the US. A practice's bundled reimbursement in the RO-APM will be closely tied to its historical reimbursements per episode of care. Practices that were early adopters of hypofractionation and high utilizers of cost-effective treatments like brachytherapy (i.e. efficient practices) will receive *lower* reimbursements than practices that have been slow adopters of hypofractionation or who have not utilized cost-effective modalities (i.e. inefficient practices) (65). The RO-APM also does not account for the cost of episodes of care that require combination modality therapies, including brachytherapy as a boost, and inadvertently incorporates palliative care episodes in calculation of bundled rates. Solutions exist that can align

incentives in the RO-APM towards high-value cancer care including brachytherapy without unfairly penalizing efficient practices – a win for patients, providers, and society.

Conclusion

Brachytherapy is vital and irreplaceable for gynecologic malignancies and results in excellent treatment and toxicity outcomes for breast and prostate malignancies. Brachytherapy is value-based and cost-effective. Utilization of brachytherapy had shown a decline in the early 2000's and had been associated with a decrease in resident brachytherapy caseload. The decline in residency brachytherapy training has been identified as a barrier to achieving brachytherapy competence and clinical independence(66). In an effort to combat the decline in brachytherapy some resident training centers have instituted brachytherapy simulation workshops to improve resident brachytherapy training(66, 67), and the American Brachytherapy Society (ABS) has called for expanded training opportunities(68). The ABS initiated a 10 year strategic program to address declining rates of brachytherapy utilization referred to as "300 in 10". The goal is to train 30 competent brachytherapists per year over 10 years through a multi-faceted approach that includes developing a national brachytherapy curriculum, simulation-based medical education, 2-month fellowships for senior level residents, a certification process, and maintenance of certification(69).

Given pre-existing inclinations for shorter radiation courses, a new radiation oncology normalcy will likely establish hypofractionated radiation as the standard of care across multiple disease sites. With shifting reimbursement, brachytherapy represents the pinnacle in hypofractionated, conformal radiation therapy with extensive long-term data in support of the treatment modality brachytherapy is primed for a renaissance.

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