Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First Community Health Choices	**Submission Date**: 1/1/2024
Policy Number: ccp.1183	**Effective Date:** 1/2016 **Revision Date:** November 1, 2023
Policy Name: Brachytherapy for cancers other than prostate	

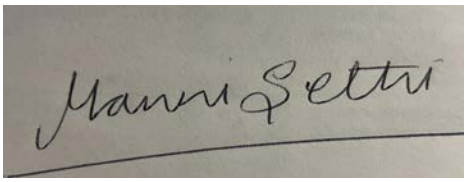
Type of Submission – Check all that apply:

New Policy
xRevised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Brachytherapy for cancers other than prostate

Clinical Policy ID: CCP.1183

Recent review date: 11/2023

Next review date: 3/2025

Policy contains: Brachytherapy.

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Brachytherapy for cancers other than prostate cancer is clinically proven and, therefore, medically necessary for treatment of the following conditions:

- Breast cancer — as an additional conformal boost to the surgical bed and margins following standard whole breast radiotherapy; or for women > 45 years of age with infiltrating ductal carcinoma who are stage T1 or T2 with no distant metastases, with tumors less than three centimeters in size and node negative (American Society of Breast Surgeons, 2018; Shah, 2013; Correa, 2017; Hepel, 2017; National Comprehensive Cancer Network, 2023).

- Genitourinary cancers (including bladder, cervical, endometrial, and uterine) — must have locally advanced cervical cancer; or as an adjunct to surgery and/or chemotherapy for advanced ovarian cancer; or as adjunctive therapy for endometrial or vaginal cancer after surgery with or without external beam radiation (Harkenrider, 2023; Meyer, 2015; National Comprehensive Cancer Network, 2023; Pieters, 2017; Viswanathan, 2009; Viswanathan, 2017).

- Respiratory cancers — when used for palliation of obstructing and inoperable endobronchial carcinomas, with or without external beam radiation (National Comprehensive Cancer Network, 2023; Rosenzweig, 2013; Stewart, 2016).

- Digestive tract cancers — palliation for obstructing esophageal cancers not considered operative candidates, endoscopically treated patients with unresectable advanced gastric carcinoma, and colon and rectal cancers (Ahmed, 2021; Lloyd, 2017; National Comprehensive Cancer Network, 2023; Spaander, 2016).

- Head, neck, and oral cancers — as primary treatment of carcinoma of the face, oral cavity, naso- and oropharynx, or paranasal sinuses (including base of skull), incomplete resections impinging on important structures, or palliation of head and neck tumors (Liu, 2013; National Comprehensive Cancer Network, 2023; Yamazaki, 2013).

- Penile cancers — for squamous cell carcinoma of the penis as an alternative to penectomy, provided there is no evidence of metastatic disease (Crook, 2013; National Comprehensive Cancer Network, 2023).

- Ocular cancers — for uveal melanoma as an alternative to enucleation or exenteration, or retinoblastoma of less than stage T4 (American Brachytherapy Society, 2014).

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Chemotherapy.
- External beam radiation.
- Radical cancer surgery.

Background

Brachytherapy (interstitial radiation) is a form of internal radiation therapy in which encapsulated sources of radiation (“seeds, ribbons or capsules”), typically radioactive iodine-125 or palladium-103, are implanted directly into or adjacent to tumor tissues, used frequently for head, eye, neck, breast, and cervical cancers as well as prostate (National Cancer Institute, 2019). Brachytherapy is based on the principle that radiation doses decrease as a function of the squared distance from the source, making it possible to deliver intensive exposure to cancerous tissue while minimizing exposure and adverse effects to surrounding healthy tissue.

Introduced in the 1960s, brachytherapy was initially used as a treatment for prostate cancer, the most common non-cutaneous malignancy in men. Since then, it has been employed to treat a variety of cancers, as well as other conditions including stenotic obstruction after lung transplant, peripheral vascular disease, and angioplasty.

Brachytherapy is one of two major therapies (the other being breast-conserving surgery) that can be used to treat early-stage breast cancer, as an alternative to mastectomy; an estimated 71,000 American women with

breast cancer are considered candidates for brachytherapy (Skowronek, 2017). For those without advanced disease, interstitial brachytherapy is implanted one week after lumpectomy, and remains in place for one week to minimize radiation exposure to the entire breast. Better results have been demonstrated in younger women than older, but overall it has shown superior cosmetic outcomes when compared to external beam radiation treatment (Mayer, 2022).

Aside from prostate and breast cancer, brachytherapy is used in the treatment of a variety of cancers (American Brachytherapy Society, 2023). The treatment can also be used in combination with surgery or external beam radiation.

Brachytherapy can employ a variety of radioactive isotopes, including palladium-103, iodine-125 (used for permanent implantation), iridium-192, and cesium-137 (used for temporary implantation).

High and low doses are used in brachytherapy. In some studies, high doses have been found to be the preferable form of treatment. High-dose therapy is associated with patient convenience, more individualized therapy, a more accurate radiation source, and greater ability to treat on an outpatient basis (Liu, 2014).

Findings

Numerous guidelines supporting use of brachytherapy for cancers other than prostate exist, and some are mentioned here. Several guidelines support brachytherapy for breast cancer. One concludes that interstitial multi-catheter brachytherapy is effective for early-stage breast cancer (Hepel, 2017). Another, from the American Brachytherapy Society, lists criteria supporting use of accelerated partial breast irradiation; criteria for most appropriate candidates are age > 45 years, all invasive histologies and ductal carcinoma in situ, tumors < 3 cm, node negative, estrogen receptor positive/negative, no lymphovascular space invasion, and negative margins (Shah, 2018). This guideline is supported by the Group Européen de Curiethérapie-European Society for Radiotherapy and Oncology/Advisory Committee on Radiation Oncology Practice (Strnad, 2018).

Guidelines for genitourinary cancers include one for bladder cancer by the Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology/Advisory Committee on Radiation Oncology Practice, as an alternative to radical cystectomy with pelvic lymph node dissection with or without neoadjuvant chemotherapy (Pieters, 2017). A task force of the American Brachytherapy Society issued recommendations for using the technique to treat cervical cancer (Viswanathan, 2009), as well as cervical and endometrial cancer (Viswanathan, 2017). An American Society for Radiation Oncology guideline strongly recommends brachytherapy for women receiving definitive radiotherapy for non-metastatic cervical cancer (Chino, 2020).

Endobronchial brachytherapy is essentially a palliative measure for treating locally advanced non-small cell lung cancer. An American Brachytherapy Society guideline supports use of endobronchial brachytherapy for disease palliation in patients with central obstructing lesions, especially in patients who have previously received external beam radiotherapy. Brachytherapy is not recommended after sub-lobar resection, except as part of a clinical trial (Stewart, 2016). An American College of Radiology guideline supports use of brachytherapy in symptomatic endobronchial tumors (Rosenzweig, 2013).

For digestive tract cancers, high-dose brachytherapy is recommended by the American Brachytherapy Society for recurrent and primary locally advanced disease, along with gynecologic cancers, soft tissue sarcoma, and some head and neck and pediatric cancers. Fractionated brachytherapy is also acceptable for digestive tract cancer (Lloyd, 2017). A guideline from the European Society of Gastrointestinal Endoscopy states that

brachytherapy can provide superior survival and quality of life compared to stents (Spaander, 2016). The American Gastroenterological Association recommends either stent insertion or brachytherapy for esophageal cancer patients who are not candidates for resection (Ahmed, 2021).

For head and neck cancers, the initial focus of brachytherapy on the cure of small tumors is now also a focus on local dose escalation complementary to external beam radiation therapy, perioperative function preservation, and treating recurrent disease (Kovacs, 2015). An American Brachytherapy Society Task Force guideline concludes the treatment is the best choice for dose escalation over a short treatment period and for minimizing radiation-related normal tissue damage due to the rapid dose falloff around the source (Takacsi-Nagy, 2017).

Research on penile cancers led the American Brachytherapy Society and the European Society of Therapeutic Radiation Oncology to recommend low doses of brachytherapy using iridium-192 for penile cancers T1, T2, and T3 (Crook, 2013). Another guideline states that penile brachytherapy can be performed under general anesthesia or penile block with systemic sedation. Low dose rate brachytherapy consists of either manually after loaded 192 Ir or pulse dose rate brachytherapy with automated after loading with a high intensity 192 Ir source to deliver hourly pulses (Van Poppel, 2013).

A guideline from the American Brachytherapy Society Ophthalmic Oncology Task Force advises that ophthalmic plaque radiation therapy is most suitable in subspecialty brachytherapy centers, by subspecialty-trained surgeons. The group agreed that most melanomas of the iris, ciliary body, and choroid, but not tumors with gross orbital extension and blind painful eyes or those with no light perception vision, can be treated with brachytherapy (American Brachytherapy Society, 2014).

The National Comprehensive Cancer Network has issued a number of guidelines, by type of cancer, supporting the use of brachytherapy for invasive breast cancer; uterine neoplasms; non-small-cell lung cancer; esophageal and esophagogastric junction cancers; head and neck cancers; colon cancer; rectal cancer; and penile cancer (National Comprehensive Cancer Network, 2023).

The following systematic reviews, meta-analyses, and other large-scale or randomized trials provide information on efficacy and safety of brachytherapy for various (non-prostate) cancers:

Breast cancer.

- A systematic review/meta-analysis of 11 randomized clinical trials (n = 14,436) of women with early breast cancer found no difference in local recurrence rates between brachytherapy and whole-breast irradiation (*P* = .51); the difference was significant when external beam radiotherapy and intraoperative radiotherapy were added to brachytherapy (*P* = .024). No difference was observed between brachytherapy and whole-breast irradiation in 10-year total mortality, along with rates of cardiac death, contralateral breast cancer, and development of second tumors (Viani, 2020).
- A review of 67 articles found that five-year local failure rates ranged from 1.4% to 6.1% for multi-catheter interstitial brachytherapy, and 0.0% to 5.7% for single-entry brachytherapy catheters. Infection rates were 0.0% to 12.0%. Symptomatic fat necrosis was documented in 0.0% to 12.0% and 0.0% to 3.2% of patients treated with the two catheters, respectively (Shaitelman, 2017).
- Long-term outcomes were studied on 157 patients receiving accelerated partial breast irradiation with balloon-and-catheter-based (MammoSite) brachytherapy after breast-conserving surgery and axillary staging. Five- and seven-year ipsilateral breast control rates were both 98%, and nodal control rates were 99% and 98%. Rates of ipsilateral breast recurrence, nodal failure, and distant failure were low

(2.5%, 1.9%, and 0.6%). Survival rates were 89% and 86% (overall) and 100% and 99% (breast cancer) (Vargo, 2014).

Genitourinary cancers.

- A systematic review of 20 articles of selected cases of muscle-invasive bladder cancer treated with brachytherapy as part of combined modality therapy (along with external beam radiotherapy) in muscle-invasive bladder cancer reported 5- and 10-year overall survival of 60% and 42%. Disease-specific survival at five years was 75% (Mannion, 2020).
- A systematic review/meta-analysis of 13 studies found that pre-operative brachytherapy for early-stage cervical cancer, compared to up-front surgery, resulted in a significantly higher five-year survival (Odds Ratio 1.78) (Vieira-Serna, 2023).
- In a systematic review of five articles (n = 463), treatment of stage II endometrial cancer with external beam radiotherapy with versus without brachytherapy resulted in no difference in overall survival (Narasimhulu, 2020).
- A systematic review/meta-analysis of 14 randomized trials of high-risk endometrial cancer (n = 5,872) analyzed improvements in adjuvant therapies versus surgery. Combined pelvic radiation therapy and vaginal brachytherapy reduced local recurrences by 85%, which exceeded reductions for pelvic radiation therapy (-67%), chemotherapy (-61%), and a combination (-83%) (Ao, 2020).
- A review of 364 women with stage I uterine serous cancer treated with adjuvant brachytherapy in addition to chemotherapy resulted in average local control 97.5%, disease free-survival 88%, overall survival 93%, specific cancer survival 89.4%, and G3-G4 toxicity 0-8% (Lancellotta, 2020a).
- A systematic review of 33 studies (n = 2,893) showed high- and intermediate-risk intermediate target volume brachytherapy for cervical cancer had greater than a 90% probability of local tumor control at doses of >84 Gy and 69 Gy, respectively (Tang, 2020).
- A review of 4,602 patients with early-stage endometrial cancer included 41% given vaginal brachytherapy and chemotherapy and 59% given pelvic radiotherapy. The brachytherapy group had a higher (*P* = .04) three-year overall survival (89.6% vs. 87.8%). Patients with serous histology experienced benefit with brachytherapy/chemotherapy, radiotherapy improved survival of high-grade endometrial patients without lymph node dissection (Tatebe, 2019).
- A group of 427 women with high/intermediate risk endometrial cancer were treated with pelvic external beam radiotherapy or with vaginal brachytherapy, and followed for a median of 9.7 years. After 10 years, the brachytherapy group had higher vaginal recurrence (3.4% versus 2.4%, *P* = .55), more frequent pelvic recurrence (6.3% versus 0.9%, *P* = .004), and higher overall survival for (69.5% versus 67.6%, *P* = .72) (Wortman, 2018).
- A review of 30 studies (n = 18,937) of women with cervical cancer given high- or low-dose brachytherapy produced similar five-year survival and disease-free survival rates (effect sizes 1.1350 and 1.0777). Pelvic recurrence and rectal or bladder complications were also similar between the two groups (Lee, 2015).
- A Cochrane review of four studies (n = 1,265 women with cancer of the uterine cervix) compared high- and low-dose rate brachytherapy (combined external beam and intracavity). Those in the high-dose group had lower overall survival rates at three, five, and 10 years (risk ratios 0.95, 0.93, and 0.79), and similar disease-specific survival rates at five and 10 years (0.95 and 1.02). The only significant difference (*P* = .04) was a higher small bowel complication rate for high-dose patients (Liu, 2014).
- A review of 24 studies (n = 892 women with pelvic malignancies undergoing transposition to preserve ovarian function) compared outcomes between those who had brachytherapy and surgery with and without external beam radiotherapy. The group that received external beam radiotherapy had a higher

rate of preserved ovarian function (94% versus 65%), a lower rate of those not developing ovarian cysts (84% versus 95%), and the same rate of those who did not suffer transposed ovary metastasis (both 100%) (Gubbala, 2014).

- A review of 19 studies (n = 672) of perineal-based interstitial brachytherapy for cervical cancer patients who received 3D image-based planning found that patients with a lower total dose had an inferior local control. Procedure-related complications were rare (seven infections and seven episodes of bleeding) and limited (Mendez, 2017). Another review of 13 studies (n = 1,299) also linked higher doses with higher chances of local control (Mazeron, 2016).
- A systematic review of 13 studies (n = 888 women age > 65 with medically inoperable endometrial cancer) showed any type of radiotherapy was more successful than no local therapy. Brachytherapy alone had a hazard ratio of 0.499, superior to external beam radiation therapy (0.694) but slightly less effective than a combination of the two (0.442) (Dutta, 2017).
- A review of 15,201 women with early stage endometrial carcinoma demonstrated that adjuvant vaginal brachytherapy is being used more often (17.1% of patients in 1995 – 2000 versus 57.1% of patients in 2007 – 2012), and the use of pelvic external beam radiation therapy is declining (54.0% to 25.5%), both significant at $P < .0001$. The use of both in the same patient also declined, from 28.9% to 17.4%, $P < .0001$ (Modh, 2016).
- A systematic review of 19 studies (n = 3,779) of muscle invasive bladder cancer, bladder sparing brachytherapy is at least as effective as the more invasive cystoscopy in terms of cause-specific survival and overall survival (Bos, 2014).

Non-small cell lung cancer.

- A meta-analysis of 15 studies (n = 1,188) compared outcomes for patients with advanced non-small cell lung cancer who were given chemotherapy with or without brachytherapy (iodine-125). The group that received brachytherapy had significantly greater response rate, disease control rate, and overall survival; significantly higher risk of pneumothorax, bloody sputum, and pneumorrhagia; and similar rates of gastrointestinal symptoms, leukopenia, myelosuppression, and hemoglobin reduction (Zhang, 2018).
- A meta-analysis of five randomized controlled trials (n = 296 patients with advanced lung cancer) compared those given chemotherapy with and without brachytherapy (iodine-125). The brachytherapy group had significantly greater complete response, partial response, overall response, disease control rate, and progressive disease (all $P < .001$). Survival was significant at one year ($P = .006$), but not two years ($P = .39$). Pneumothorax was the only adverse event that was significantly higher in the brachytherapy group ($P = .001$) (Qiu, 2017).
- A literature review concluded that brachytherapy had low recurrence rate with low toxicity after adjuvant therapy to sublobar resection for lung cancer due to poor cardiopulmonary reserve. Ten articles of palliative brachytherapy showed symptomatic improvement with good tolerance and good endoscopic response rates (Youroukou, 2017).

Digestive tract cancers.

- A systematic review of 12 studies of operable rectal cancer compared high-dose pre-operative brachytherapy with and without chemoradiation. Brachytherapy alone was similar to combination therapy in pathologic complete response (weighted mean rate 23.8% versus 22.2%); R0 resection rate (96.5% versus 95.5%); and sphincter-preservation rate (59.4% versus 46.4%). Overall survival for

brachytherapy alone was lower (70.8% versus 81.5%), as was progression-free survival (66.6% versus 68.1%) (Buckley, 2017).

- A systematic review of 12 studies (n = 514) analyzed safety and effectiveness of brachytherapy, alone or combined with external beam radiotherapy, for stage I esophageal cancer. Results were supportive, i.e., median: local control = 77%; disease-free survival = 68.4%; overall survival = 60%; cancer specific survival = 80%; and grade 3-4 toxicity was 0%-26% (Lancellotta, 2020b).
- A systematic review of seven studies (n = 905) assessed safety and efficacy of palliative brachytherapy in esophageal cancer versus other treatment. In the brachytherapy group, median dysphagia-free and overall survival were 99 and 175.5 days, and the most relevant G3-G4 toxicity were fistula development and stenosis, in 8.3% and 12.2% of cases (Lancellotta, 2020c).
- A systematic review of six studies (n = 623) addressed the palliation of dysphagia in esophageal cancer with brachytherapy. Dysphagia-free survival rates one, three, six, nine, and 12 months after treatment were 86.9%, 67.2%, 47.4%, 37.6%, and 29.4%, respectively. The severe adverse events rate was 22.6%. The authors concluded that brachytherapy should be used for dysphagia in patients with esophageal cancer (Fuccio, 2017).
- A Cochrane review of 53 studies (n = 3,684) found that for palliation of dysphagia in patients with esophageal cancer, brachytherapy may be a suitable alternative to self-expanding metallic stents (Dai, 2014).
- A systematic review/meta-analysis included two studies (n = 274) of safety of stents versus brachytherapy for patients with inoperable esophageal cancer. Brachytherapy had a lower risk of fistula formation and hemorrhage, but a higher risk of perforation (Lai, 2018).
- A systematic review of 38 studies (n = 3,862) of patients who underwent endorectal radiation for rectal cancer reported rectal toxicity in 6.3% of brachytherapy patients, significantly higher than 2.9% for contact X-ray therapy patients (Verrijssen, 2019).

Head, neck, and oral cancers.

- A meta-analysis of six trials (n = 607) of early-stage oral cancer compared outcomes after low- and high-dose brachytherapy. No significant differences were observed between the groups for local recurrence (odds ratio = 1.12), overall mortality (1.01), and grade 3/4 complications (0.86). Authors contend that high-dose brachytherapy is a comparable alternative to low doses, and may eventually become a routine choice (Liu, 2013).
- A literature review asserts that while low doses were originally used in treating head and neck cancer with brachytherapy, initial experience with high-dose treatment is a viable option (Yamazaki, 2013).
- A systematic review of 30 studies of treatment for recurrent head and neck cancers found brachytherapy to be most effective (greater local control and overall survival) when administered adjunctive to surgical resection versus brachytherapy alone (Rodin, 2018).

Penile cancer.

- A lengthy literature review determined that low-dose brachytherapy using iridium-192 results in a 10-year penile preservation rate of 70% (Crook, 2013).
- A meta-analysis of 22 studies (n = 2,560) compared brachytherapy and penectomy for patients with penile cancer. The penectomy group had superior rates of five-year local control (85% versus 80%), five-year disease-free progression (77% versus 72%), and lymph node positive rates (24% versus 20%). No significant difference was observed for five-year survival rate (76% versus 74%) (Hu, 2017).

- A meta-analysis on penile cancer compared 1,505 men who had penectomy with 673 who had brachytherapy. Brachytherapy patients had an insignificantly lower five-year survival (73% versus 76%, *P* < .13). The penectomy group had a higher five-year local control rate (84% versus 79%, *P* = .009). No significant difference was observed for overall survival or local control for early stage disease (Hasan, 2015).

Ocular cancers.

- A systematic review and meta-analysis comparing charged particle therapy with brachytherapy for uveal melanomas included 27 studies (n = 8,809). The local recurrence rate for charged particle therapy was significantly lower (odds ratio = 0.22), as were retinopathy and cataract formation rates. No significant differences existed for mortality or enucleation rates. The quality of evidence is low, suggesting more and better evidence is needed (Wang, 2013).
- A systematic review of 15 studies (n = 2,662) of iodine-125 brachytherapy for uveal melanoma revealed a dose range of 62.5 – 104 gray (average 85), and local recurrence rates ranging from 0.0% to 24.0%. A 1-gray increase in average study dose was associated with a 0.14% decrease in local recurrence rate, not significant (*P* = .336) (Echegaray, 2017).

References

On August 24, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “brachytherapy, radiation therapy, radiation seed implants.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Ahmed O, Lee JH, Thompson CC, Faulx A. AGA clinical practice update on the optimal management of the malignant alimentary tract obstruction: Expert review. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21)00381-5. Doi: 10.1016/j.cgh.2021.03.046.

American Brachytherapy Society. Current Applications of Brachytherapy. https://www.americanbrachytherapy.org/resources/for-professionals/current-applications-of-brachytherapy/. Published 2023.

American Brachytherapy Society – Ophthalmic Oncology Task Force. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy*. 2014;13(1):1-14. Doi: 10.1016/j.brachy.2013.11.008.

American Society of Breast Surgeons. Consensus statement for accelerated partial breast irradiation. https://www.breastsurgeons.org/docs/statements/Consensus-Statement-for-Accelerated-Partial-Breast-Irradiation.pdf. Updated June 5, 2018.

Ao M, Ding T, Tang D, Xi M. Efficacy and toxicity of adjuvant therapies for high-risk endometrial cancer in Stage I-III: A systematic review and network meta-analysis. *Med Sci Monit*. 2020;26:e925595. Doi: 10.12659/MSM.925595.

Bos MK, Marmolejo RO, Rasch CR, Pieters BR. Bladder preservation with brachytherapy compared to cystectomy for T1-T3 muscle-invasive bladder cancer: A systematic review. *J Contemp Brachytherapy*. 2014;6(2):191-199. Doi: 10.5114/jcb.2014.43777.

Buckley H, Wilson C, Ajithkumar T. High-dose-rate brachytherapy in the management of operable rectal cancer: A systematic review. *Int J Radiat Oncol Biol Phys*. 2017;99(1):111-127. Doi: 10.1016/j.ijrobp.2017.05.023.

Chino J, Annunziata CM, Beriwal S, et al. Radiation therapy for cervical cancer: Executive summary of an ASTRO clinical practice guideline. *Pract Radiat Oncol*. 2020;10(4):220-234. Doi: 10.1016/j.prro.2020.04.002.

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(2):73-79. Doi: 10.1016/j.prro.2016.09.007.

Crook JM, Haie-Meder C, Demanes DJ, Mazeron JJ, Martinez AA, Rivard MJ. American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. *Brachytherapy*. 2013;12(3):191-198. Doi: 10.1016/j.brachy.2013.01.167.

Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in oesophageal cancer. *Cochrane Database Syst Rev*. 2014 Oct 30;(10):CD005048. Doi: 10.1002/14651858.CD005048.pub4.

Dutta SW, Trifiletti DM, Grover S, Boimel P, Showalter TN. Management of elderly patients with early-stage medically inoperable endometrial cancer: Systematic review and National Cancer Database analysis. *Brachytherapy*. 2017;16(3):526-533. Doi: 10.1016/j.brachy.2017.01.011.

Echegaray JJ, Bechrakis NE, Singh N, Bellerive C, Singh AD. Iodine-125 brachytherapy for uveal melanoma: A systematic review of radiation dose. *Ocul Oncol Pathol*. 2017;3(3):193-198. Doi: 10.1159/000455872.

Fuccio L, Mandolesi D, Farioli A, et al. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: A systematic review and meta-analysis of prospective studies. *Radiother Oncol*. 2017;122(3):332-339. Doi: 10.1016/j.radonc.2016.12.034.

Gubbala K, Laios A, Gallos I, Patthiraia P, Haldar K, Ind T. Outcomes of ovarian transposition in gynaecological cancers: A systematic review and meta-analysis. *J Ovarian Res.* 2014;7:69. Doi: 10.1186/1757-2215-7-69.

Harkenrider MH, Abu-Rustum N, Albuquerque K, et al. Radiation therapy for endometrial cancer: An American Society for Radiation Oncology clinical practice guideline. *Pract Radiat Oncol*. 2023;13(1):41-65. Doi: 10.1016/j.prro.2022.09.002.

Hasan S, Francis A, Hagenauer A, et al. The role of brachytherapy in organ preservation for penile cancer: A meta-analysis and review of the literature. *Brachytherapy*. 2015;14(4):517-524. Doi: 10.1016/j.brachy.2015.03.008.

Hepel JT, Arthur D, Shaitelman S, et al. American Brachytherapy Society consensus report for accelerated partial breast irradiation using interstitial multicatheter brachytherapy. *Brachytherapy*. 2017;16(5):919-928. Doi: 10.1016/j.brachy.2017.05.012.

Hu X, Huang J, Wen S, Fu J, Chen M. Comparison of efficacy between brachytherapy and penectomy in patients with penile cancer: A meta-analysis. *Oncotarget*. 2017;8(59):100469-100477. Doi: 10.18632/oncotarget.18761.

Kovacs G. Modern head and neck brachytherapy: From radium towards intensity modulated interventional brachytherapy. *J Contemp Brachytherapy*. 2015;6(4):404-416. Doi: 10.5114/jcb.2014.47813.

Lai A, Lipka S, Kumar A, et al. Role of esophageal metal stents placement and combination therapy in inoperable esophageal carcinoma: A systematic review and meta-analysis. *Dig Dis Sci*. 2018;63(4):1025-1034. Doi: 10.1007/s10620-018-4957-z.

Lancellotta V, De Felice F, Vicenzi L, et al. The role of vaginal brachytherapy in stage I endometrial serous cancer: A systematic review. *J Contemp Brachytherapy*. 2020a;12(1):61-66. Doi: 10.5114/jcb.2020.92698.

Lancellotta V, Cellini F, Fionda B, et al. The role of interventional radiotherapy (brachytherapy) in stage I esophageal cancer: An AIRO (Italian Association of Radiotherapy and Clinical Oncology) systematic review. *Eur Rev Med Pharmacol Sci* . 2020b;24(14):7589-7597. Doi: 10.26355/eurrev_202007_22257.

Lancellotta V, Cellini F, Fionda B, et al. The role of palliative interventional radiotherapy (brachytherapy) in esophageal cancer: An AIRO (Italian Association of Radiotherapy and Clinical Oncology) systematic review focused on dysphagia-free survival. *Brachytherapy*. 2020c;19(1):104-110. Doi: 10.1016/j.brachy.2019.09.005.

Lee KK, Lee JY, Nam JM, Kim CB, Park KR. High-dose-rate vs. low-dose-rate intracavitary brachytherapy for carcinoma of the uterine cervix: Systematic review and meta-analysis. *Brachytherapy*. 2015;14(4):449-457. Doi: 10.1016/j.brachy.2015.02.390.

Liu R, Wang X, Tian JH, et al. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer. *Cochrane Database of Syst Rev*. 2014;(10):CD007563. Doi: 10.1002/14651858.CD007563.pub3.

Liu Z, Huang S, Zhang D. High dose rate versus low dose rate brachytherapy for oral cancer — a meta-analysis of clinical trials. *PLoSOne.* 2013;8(6):e65423. Doi: 10.1371/journal.pone.0065423.

Lloyd S, Alektiar KM, Nag S, et al. Intraoperative high-dose-rate brachytherapy: An American Brachytherapy Society consensus report. *Brachytherapy*. 2017;16(3):446-465. Doi: 10.1016/j.brachy.2017.01.001.

Mannion L, Bosco C, Nair R, et al. Overall survival, disease-specific survival, and local recurrence outcomes in patients with muscle-invasive bladder cancer treated with external beam radiotherapy and brachytherapy: A systematic review. *BJU Int*. 2020;125(6):780-791. Doi: 10.1111/bju.15047.

Mayer C, Kumar A. Brachytherapy. https://www.ncbi.nlm.nih.gov/books/NBK562190/. Updated September 12, 2022.

Mazeron R, Castelnau-Marchand P, Escande A, et al. Tumor dose-volume response in image-guided adaptive brachytherapy for cervical cancer: A meta-regression analysis. *Brachytherapy*. 2016;15(5):537-542. Doi: 10.1016/j.brachy.2016.05.009.

Mendez LC, Weiss Y, D'Souza D, Ravi A, Barbera L, Leung E. Three-dimensional-guided perineal-based interstitial brachytherapy in cervical cancer: A systematic review of technique, local control and toxicities. *Radiother Oncol*. 2017;123(2):312-318. Doi: 10.1016/j.radonc.2017.03.005.

Meyer LA, Bohlke K, Powell MA, et al. Postoperative radiation therapy for endometrial cancer: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology evidence-based guideline. *J Clin Oncol*. 2015;33(26):2908-2913. Doi: 10.1200/JCO.2015.62.5459.

Modh A, Ghanem AI, Burmeister C, Rasool N, Elshaikh MA. Trends in the utilization of adjuvant vaginal brachytherapy in women with early-stage endometrial carcinoma: Results of an updated period analysis of SEER data. *Brachytherapy*. 2016;15(5):554-561. Doi: 10.1016/j.brachy.2016.06.012.

Narasimhulu DM, Cope A, Birz IB, et al. External beam radiotherapy versus vaginal brachytherapy in patients with stage II endometrial cancer: A systematic review and meta-analysis. *Int J Gynecol Cancer*. 2020;30(6):797-805. Doi: 10.1136/ijgc-2020-001199.

National Cancer Institute. Brachytherapy to treat cancer. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/brachytherapy#:~:text=Brachytherapy%20is%20a%20type%20of%20internal%20radiation%20that%20uses%20radiation,in%20or%20near%20the%20cancer. Updated January 29, 2019.

National Comprehensive Cancer Network. www.nccn.org. Breast cancer, version 4.2023, March 23, 2023. Colon cancer, version 2.2023, April 25, 2023. Esophageal and esophagogastric junction cancers, version 2.2023, March 10, 2023. Head and neck cancers, version 2.2023, May 15, 2023. Non-small cell lung cancer, version 3.2023, April 13, 2023. Penile cancer, version 1.2023, December 1, 2022. Rectal cancer, version 4.2023, July 25, 2023. Soft tissue sarcoma, version 2.2023, April 25, 2023. Uterine neoplasms, version 2.2023, April 28, 2023.

Qiu H, Ji J, Shao Z, et al. The efficacy and safety of Iodine-125 brachytherapy combined with chemotherapy in treatment of advanced lung cancer: A meta-analysis. *J Coll Physicians Surg Pak*. 2017;27(4):237-245. Doi: 2597.

Pieters BR, van der Steen-Banasik E, Smits GA, DeBrabandere M, Bossi A, Van Limbergen E. GEC-ESTRO/ACROP recommendations for performing bladder-sparing treatment with brachytherapy for muscle-invasive bladder carcinoma. *Radiother Oncol*. 2017;122(3):340-346. Doi: 10.1016/j.radonc.2016.12.022.

Rodin J, Bar-Ad V, Cognetti D, et al. A systematic review of treating recurrent head and neck cancer: A reintroduction of brachytherapy with or without surgery. *J Contemp Brachytherapy*. 2018;10(5):454-462. Doi: 10.5114/jcb.2018.79399.

Rosenzweig KE, Chang JY, Chetty IJ, et al. ACR appropriateness criteria nonsurgical treatment for non-small-cell lung cancer: Poor performance status or palliative intent. *J Am Coll Radiol*. 2013;10(9):654-664. Doi: 10.1016/j.jacr.2013.05.031.

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 breast brachytherapy registry trial. *Ann Surg Oncol*. 2013;20(10):3279-3285. Doi: 10.1245/s10434-013-3158-4.

Shah C, Vicini F, Shaitelman SF, et al. The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation. *Brachytherapy*. 2018;17(1):154-170. Doi: 10.1016/j.brachy.2017.09.004.

Skowronek J. Current status of brachytherapy in cancer treatment – short overview. *J Contemp Brachytherapy*. 2017;9(6):581-589. Doi: 10.5114/jcb.2017.72607.

Shaitelman SF, Amendola B, Khan A, et al. American Brachytherapy Society Task Group Report: Long-term control and toxicity with brachytherapy for localized breast cancer. *Brachytherapy*. 2017;16(1):13-21. Doi: 10.1016/j.brachy.2016.04.392.

Spaander MC, Baron TH, Siersema PD, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*. 2016;48(10):939-948. Doi: 10.1055/s-0042-114210.

Stewart A, Parshar B, Patel M, et al. American Brachytherapy Society consensus guidelines for thoracic brachytherapy for lung cancer. *Brachytherapy.* 2016;15(1):1-11. Doi: 10.1016/j.brachy.2015.09.006.

Strnad V, Major T, Polgarc C, et al. ESTRO-ACROP guideline: Interstitial multi-catheter breast brachytherapy as Accelerated Partial Breast Irradiation alone or as boost – GEC-ESTRO Breast Cancer Working Group practical recommendations. *Radiother Oncol*. 2018;128(3):411-420. Doi: 10.1016/j.radonc.2018.04.009.

Takacsi-Nagy Z, Martinez-Mongue R, Mazeron J-J, Ander CJ, Harrison LB. American Brachytherapy Society Task Group Report: Combined external beam irradiation and interstitial brachytherapy for base of tongue tumors and other head and neck sites in the era of new technologies. *Brachytherapy*. 2017;16(1):44-58. Doi: 10.1016/j.brachy.2016.07.005

Tang X, Mu X, Zhao Z, Zhao H, Mao Z. Dose-effect response in image-guided adaptive brachytherapy for cervical cancer: A systematic review and meta-regression analysis. *Brachytherapy*. 2020;19(4):438-446. Doi: 10.1016/j.brachy.2020.02.012.

Tatebe K, Hasan Y, Son CH, et al. Adjuvant vaginal brachytherapy and chemotherapy versus pelvic radiotherapy in early-stage endometrial cancer: Outcomes by risk factors. *Gynecol Oncol*. 2019;155(3):429-435. Doi: 10.1016/j.ygyno.2019.09.028.

Van Poppel H, Watkin NA, Osanto S, Moonen L, Horwich A, Kataja V; ESMO Guidelines Working Group. Penile cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi115-24. Doi: 10.1093/annonc/mdt286.

Vargo JA, Verma V, Kim H, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: Patterns of failure, patient selection, and dosimetric correlates for late toxicity. *Int J Radiat Oncol Biol Phys*. 2014;88(2):285-291. Doi: 10.1016/j.ijrobp.2013.05.039.

Verrijssen AS, Opbroek T, Bellezzo M, et al. A systematic review comparing radiation toxicity after various endorectal techniques. *Brachytherapy*. 2019;18(1):71-86.e5. Doi: 10.1016/j.brachy.2018.10.001.

Viani GA, Arruda CV, Faustino AC, De Fendi LI. Partial-breast irradiation versus whole-breast radiotherapy for early breast cancer: A systematic review and update meta-analysis. *Brachytherapy*. 2020;19(4):491-498. Doi: 10.1016/j.brachy.2020.03.003.

Vieira-Serna S, Viveros-Carreno D, Rodriguez J, et al. Preoperative brachytherapy for early-stage cervical cancer: Systematic review and meta-analysis. *Gynecol Oncol*. 2023;169:4-11. Doi: 10.1016/j.ygyno.2022.11.009.

Viswanathan AN, Erickson BA, Ibbott GS, Small W Jr, Eifel PJ. The American College of Radiology and the American Brachytherapy Society practice parameter for the performance of low-dose-rate brachytherapy. *Brachytherapy*. 2017;16(1):68-74. Doi: 10.1016/j.brachy.2016.06.013.

Viswanathan AN, Thomadsen B. Brachytherapy Task Group. American Brachytherapy Society. https://www.americanbrachytherapy.org/ABS/document-server/?cfp=ABS/assets/File/public/consensus-statements/cervical_cancer_taskgroup.pdf. Published 2009.

Wang Z, Nabhan M, Schild SE, et al. Charged particle radiation therapy for uveal melanoma: A systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys*. 2013;86(1):18-26. Doi: 10.1016/j.ijrobp.2012.08.026.

Wortman BG, Creutzberg CL, Putter H, et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: Improving patient selection for adjuvant therapy. *Br J Cancer*. 2018;119(9):1067-1074. Doi: 10.1038/s41416-018-0310-8.

Yamazaki H, Yoshida K, Yoshioka Y, Shimizutani K, Furukawa S, Koizumi M, Ogawa K. High dose rate brachytherapy for oral cancer. *J Radiat Res*. 2013;54(1):1-17. Doi: 10.1093/jrr/rrs103.

Youroukou A, Gkiozos I, Kalaitzi Z, et al. The potential role of brachytherapy in the irradiation of patients with lung cancer: A systematic review. *Clin Transl Oncol*. 2017;19(8):945-950. Doi: 10.1007/s12094-017-1635-0.

Zhang W, Li J, Li R, Zhang Y, Han M, Ma W. Efficacy and safety of iodine-125 radioactive seeds brachytherapy for advanced non-small cell lung cancer-A meta-analysis. *Brachytherapy*. 2018;17(2):439-448. Doi: 10.1016/j.brachy.2017.11.015.

Policy updates

8/2015: initial review date and clinical policy effective date: 1/2016

8/2016: Policy references updated.

8/2017: Policy references updated.

8/2018: Policy references updated.

11/2019: Policy references updated. Policy ID changed to CCP.1183.

11/2020: Policy references updated.

11/2021: Policy references updated.

11/2022: Policy references updated.

11/2023: Policy references updated.