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Health Services Research in brachytherapy: current understanding and future challenges

List of acronym

BT - Brachytherapy
BTU – Brachytherapy Utilisation rate
CEA – Cost-effectiveness analysis
CUA – Cost-utility analysis
EBRT – External Beam Radiotherapy
HDR – High Dose Rate
LDR – Low Dose Rate
NHS – National Health Service
NICE – National Institute of Health and Care Excellence
QALY – Quality Adjusted Life Year
RTU – Radiotherapy Utilisation RATE
TD-ABC – Time-Driven Activity-Based Costing

Introduction

Brachytherapy (BT) is an important treatment option for a range of cancer diagnoses. Concerns are, however, frequently raised about falling availability of brachytherapy across jurisdictions. Yet unlike in external beam radiotherapy (EBRT), there has been relatively little work undertaken to understand its use from a health services perspective [1]. Such work is crucial to determining the extent to which current services address the population need, what the scale of this need is, what investment is required to deliver these interventions and finally, whether this investment would offer value to the wider health service through the delivery of increased population health. In this review we will discuss the current literature in this area and highlight where further work is required.

Brachytherapy is an integral component of cancer guidelines, including the "Groupe Européen de Curiethérapie" - European SocieTy for Radiotherapy and Oncology(GEC-ESTRO) [2], the National Comprehensive Cancer Network (NCCN), USA [3-5], the American Brachytherapy Society (ABS) [6-10], and Cancer Institute, New South Wales in Australia [11, 12]. Extensive observational data and subsequent randomised studies support the use of brachytherapy in the treatment of cervix and endometrial cancers [13-19]. Gill et al. found that in 7,654 patients receiving radiotherapy for advanced cervical cancer, overall survival was inferior with IMRT/SBRT compared with a brachytherapy boost [20]. Similarly, for patients with early-stage endometrial cancer, the PORTEC 2 trial demonstrated excellent local control with vaginal brachytherapy versus external beam radiotherapy [16, 21].

Brachytherapy is also an important treatment option for patients with prostate cancer. Here, randomised data supporting its use is more limited and spread more thinly across a more heterogeneous population [19, 22, 23]. The ASCENDE-RT trial demonstrated a reduction in biochemical failure for patients with intermediate and high-risk prostate cancer who received a brachytherapy boost (low dose rate (LDR)) compared with dose escalated EBRT [22]. Hoskin et al. also demonstrated an improvement in relapse free survival with a high dose rate (HDR) boost for patients with localised prostate cancer [23].

In an era of increasingly conformal EBRT, in some centres, brachytherapy has been replaced by image guided radiotherapy with intensity-modulated radiotherapy (IMRT), volumetric-arc therapy (VMAT) or indeed, stereotactic techniques [5, 23-27]. Conversely, beyond these major indications, brachytherapy (BT) is used, albeit less commonly for various other tumour sites. These include: skin cancers; intraluminal brachytherapy for rectal cancer and obstructive lung or localised oesophageal tumours; ocular tumours, head and neck cancers; and post/intra operative partial breast irradiation (23, 24). Here, we will focus predominantly on the most common brachytherapy indications. We will consider expected and observed brachytherapy utilisation, the resources required to deliver BT and the evidence available to assess its cost-effectiveness. Finally, we will discuss how research in these areas could be used to ensure brachytherapy is available for all patients who require it.

Optimal Brachytherapy Utilisation Rates (BTU)

Evidence-based guidelines and epidemiological data have been used to estimate the proportion of patients expected to benefit from receiving brachytherapy, providing an *optimal* BT utilisation rate (BTU). The optimal BTU is defined by Thompson et al as the 'proportion of patients that should have brachytherapy at least once during the course of their illness' [28-30].

The team at the Collaboration for Cancer Outcomes Research and Evaluation (CCORE) in New South Wales, Australia estimated the optimal BTU rate for patients with cervical, uterine and prostate cancer,[28-30] identifying rates of 49% [28], 40% [29] 9.6% [30] respectively. These estimates are, however, based on guidelines published more than 10 years ago and the stage distribution seen in their local population. Further estimates of optimal BTU in India have been used to explore the apparent deficiency of brachytherapy utilisation for cervical cancer. Here an optimal BTU of 85% was assumed based on available information on stage distribution [31]. It should be noted that there are limitations to the methodology for calculating the *optimal* BTU given the limited high-level evidence for BT indications and contraindications, lack of patient specific details (for patients with gynaecological malignancies) and, importantly, patient treatment preferences (for patients with prostate cancer). Beyond these major diagnoses, such uncertainties become even greater. For example, in skin cancer, dosimetric considerations become crucial, making estimation of the *optimal* BTU rate all but impossible. To our knowledge, *optimal* BTU has not been defined in other jurisdictions. An ESTRO-HERO analysis of Radiotherapy Utilisation (RTU) for EBRT in European countries [32] was performed by Borras et al, whilst a similar analysis of the BTU has been deemed feasible yet too challenging based on the above listed reasons [33].

For patients with cervical cancer in low and middle-income countries, the health and economic benefits have also been studied [34]. Rodin et al. demonstrated that 11.4 million life years would be gained with radiotherapy services scaled up to provide the recommended optimal RTU [35]. This estimate for the benefit of radiotherapy services (both EBRT and brachytherapy) has been provided in the era of Human Papilloma Virus vaccination and demonstrated the cost effectiveness of greater brachytherapy availability for cervix cancer in low and middle-income countries [35]. The challenges of implementing this are not inconsiderable with centralised services being more achievable to deliver but requiring extensive networks to support identification and treatment of patients from across large geographical areas with often limited transport infrastructure [31].

Observed Brachytherapy Utilisation Rates – Variation in practice

Few studies have reported *observed* BTU rates, with those addressing this question using differing methodologies to calculate the BTU, making direct comparisons challenging. Table 1 presents the results of studies carried out in Europe, Australia, North America, Canada and Korea.

	Tumour site	Brachytherapy utilisation	Methodology
Europe	Gynaecological malignancies	1997-2002: 60.8% (UK) [36] 1997-2002:59.7% (Spain)	Defined as the % cases receiving brachytherapy according to tumour site
	Prostate	1997-2002:13.4% (UK) 1997-2002:16.3% (Spain)	Defined as the % cases receiving brachytherapy according to tumour site
	All tumour sites	2018 (Belgium) 28% prostate seed implant 8% ocular BT 64% HDR/PDR BT [37] HDR/PDR: 45% vaginal dome BT 22% intra-uterine BT [37]	Defined as the % cases receiving brachytherapy according to tumour site
Australia – NSW	Cervix	2003: 30% [28]	Defined as the % of patients receiving brachytherapy during the course of their illness
	Endometrium	2003: 14% [29]	Defined as the % of patients receiving brachytherapy during the course of their illness
	Prostate	2003: 3.9% [30]	Defined as the % of patients receiving brachytherapy during the course of their illness

United States of America	Cervix	58% [13]	Defined as the % of patients who receive brachytherapy in addition to external beam radiotherapy
	Cervix	96.7% to 86.1% (from 2004 to 2011) [20]	Defined as the % of patients receiving brachytherapy as opposed to IMRT/SABR as their boost
	Prostate (intermediate and high risk)	27.6% and 10.8% respectively [38]	Defined as the % of patients who receive brachytherapy in addition to external beam radiotherapy
	Prostate	20% brachytherapy alone 14% with brachytherapy and EBRT [39]	Defined as the % of patients that received brachytherapy
Canada - Quebec	All tumour sites	4829 treatments in 2019 (compared to 3930 in 2011) [40]	Defined as the number of brachytherapy treatments
Korea	Cervix	84% (2005) – 78% (2013) [41]	Defined as the 'proportion of patients who received brachytherapy among those who received curative EBRT'

Table 1: Global Radiotherapy utilisation

Health economics in Brachytherapy

Cost-effectiveness analyses (CEA) aim to assess the cost of delivering a desired outcome, measured in the natural unit of the outcome (e.g. toxicity spared at one year). With the incorporation of survival and quality of life data, the cost to deliver an extra quality adjusted life year (QALY) can be determined (cost-utility analysis (CUA)). The use of the QALY measure in the latter means the value (cost per QALY) of the intervention can be considered in the context of the wider healthcare budget where the opportunity cost of investment is likely to lie outside of cancer care. This enables the decision maker to determine if investment in a novel intervention would be expected to deliver greater health benefit within a finite healthcare budget [42]. In both cases the threshold for reimbursement will vary between healthcare jurisdictions, in line with the expected health benefit delivered by the resources foregone within the system [43].

From this it is clear that information informing not only the clinical benefits of brachytherapy, but also the costs, are needed to deliver such analyses. Whilst in the health technology appraisal of pharmaceuticals the cost of the drug is the principle element, with a modest contribution from delivery, the cost of radiotherapy is more challenging to determine. Here commonly, and appropriately, costs are based on reimbursement tariffs [44] however, reimbursement tariffs may include incentives to drive clinical practise and may not align with provider expenditure [45, 46]. As such, further valuable information may be gained by understanding the costs to the provider.

Resource planning and cost estimation

Time-Driven Activity Based Costing (TD-ABC) has been widely used to determine the provider-level cost of EBRT [47, 48]. This approach identifies all activities contributing to a treatment course, the resources required to deliver each one and its necessary time and resource cost [49]. With BT delivery requiring a highly specialized team, personnel has been identified as both the main resource requirement and determinant of brachytherapy cost for both breast and prostate cancer; it accounts for at least half of the total treatment cost [50-52]. Estimating the personnel costs can, however, be challenging; high training requirements for brachytherapy may be expected to result in a significant learning curve effect with additional cost associated with training and accreditation [53]. Beyond this, equipment costs are none the less significant, with these including both disposable items (the second largest share of treatment cost in HDR and LDR, between one third to almost half of the total cost) and significant capital investment [51, 52]. Theatre space costs may vary greatly across settings; whether being dedicated for BT or shared within a general hospital, the cost per minute will be greatly influenced by idle capacity. As such, estimating an overall cost, even within a single jurisdiction, is challenging due to varying approaches, patient volumes, the learning curve and centralisation of services. Understanding this is, however, crucial to both service planning and health economic analyses.

From the provider perspective fixed, upfront capital costs and semi-variable staff costs are critical. Where the volume of BT is limited due to small, or indeed, uncertain numbers of referrals these provider costs will persist in the medium to long-term irrespective of activity. These may act as a barrier to investment and BT delivery, particularly where it is perceived that a lower reimbursement is available as compared to EBRT [1, 46]. Further, whilst in the UK the profitability of service delivery is not routinely considered, this is not true universally [54]. TD-ABC can inform a business case for brachytherapy.

Cost-effectiveness

The limitations of both clinical effectiveness and cost data have been outlined above, however, both are required for cost-effectiveness analyses (CEA). Literature searches (including search terms "brachytherapy" and cost-effect*") identified a limited number of cost-effectiveness studies, conducted in various jurisdictions for a range of clinical indications. Of the 32 primary studies, 24 originated in North America and seven in Europe, of which two (CUAs in rectal and breast cancer) took an NHS perspective [55, 56]. Studies considered prostate (nine), breast (eight), cervix (three), endometrial (three) and oesophageal (three) cancers with others assessing infrequent and investigational indications. Whilst a majority of studies were CUA/CEA's (28/32), unfortunately even amongst cost-utility analyses, study quality was often limited with parametric inaccuracies seen in some studies (e.g. expert consensus for costs incorporated rather than available reimbursement tariff), standard of care regimens not always aligning to best practise and limited studies reporting in line with consensus guidelines [57]. Additionally, there was a heavy reliance on observational data and expert consensus resulting in a significant risk of bias.

Brachytherapy cost-effectiveness varied across indications and jurisdictions. Based only on cost-utility analyses, the considered brachytherapy approaches were reported to be cost-effective in studies looking at gynaecological indications and a majority of those in prostate cancer whilst the results in breast cancer were considerably more mixed. Three systematic reviews considered the cost-effectiveness of brachytherapy in prostate cancer, concluding that limited data existed to address their specific questions [58-60]. As such, whilst a small number of subjectively strong studies exist, it is not possible to draw a firm conclusion about the cost-effectiveness of brachytherapy for any specific indication, much less to make any general statement of cost-effectiveness.

This challenge is further exacerbated by the diversity of decision problems considered and the jurisdiction specific nature of cost-effectiveness analyses. This latter is particularly problematic due to the widely differing costs of treatment and follow-up, differing methodological approaches to CEA, and varying willingness to pay thresholds accepted across jurisdictions [61]. Extrapolation of cost-effectiveness results between jurisdictions cannot be justified without careful consideration of these differences. Indeed, in the context of brachytherapy, where the practicalities of source replacement may influence the installed technology (e.g. Iridium-192 versus Cobalt-60), particularly in low and middle income countries, such differences can be further magnified [62].

Beyond the limitations to cost-effectiveness analyses detailed above it is also challenging to determine the relevance of these results for individual services and countries; centralisation of services, not possible across all jurisdictions, may result in economies of scale dramatically shifting the cost, and thus cost-effectiveness, of brachytherapy in any given indication [31]. Such centralisation may enable implementation, but the risk of inequitable access needs to be minimised through robust collaborative networks, sharing resources for the benefit of patients dispersed across a wide geographical area. This approach has been highlighted in India and may be of relevance across jurisdictions from the whole of the income scale [31].

Centralisation and economies of scale are not only relevant when considering the cost-effectiveness of new services but also in optimising, extending and modifying existing ones. The studies identified here have appropriately taken a payer perspective with a minority incorporating provider-level cost. Scenario analyses incorporating the latter may, however, be informative; the marginal cost of treatment within existing capacity will differ considerably from that of implementation requiring further capital investment [63]. This is particularly important given that in many jurisdictions the financial case for brachytherapy investment will be made at a provider level, necessitating that any financial case recognises this perspective alongside that of the wider health service.

The question of whose perspective should be taken has also been highlighted where patient costs have been considered; a single treatment visit is undoubtedly more convenient and less costly for the patient than attending for multiple EBRT fractions (although as ultrahypofractionation of EBRT becomes more widely accepted this difference diminishes) [64]. Additionally, a patient perspective may also be required in the valuation of quality of life. The approach taken to this varies between jurisdictions. In England the National Institute of Health and Care Excellence (NICE) defines the value attributed to each health state (and thus the calculation of QALYs) based on how a representative national population value these health states [65]. Where the side-effect profiles of the different interventions vary widely, these average values may not be a good representation of what each individual wishes to prioritise. As such, where the interventions offer similar net health benefit it maybe appropriate to provide access to all options, supported by a shared-decision making approach.

Discussion

Concerns have been raised by many groups about variation in brachytherapy utilisation and, in places, a lack of brachytherapy utilisation [1, 13, 31, 38]. One reason for this discrepancy between expected and observed utilisation may be the perceived costs of a brachytherapy program. Limited randomised data exist informing the clinical benefits of brachytherapy, yet it is time and resource intensive. In addition, technological advancement in EBRT presents evolving competition to brachytherapy making the case for investment more uncertain. All of these uncertainties are exacerbated by a paucity of health services research in this area.

Concern about the financial and infrastructure requirements of brachytherapy mirror those of workforce planning and availability. A review paper by Banerjee et al. on brachytherapy in India highlights the technical personnel requirements and the importance of brachytherapy specific training and educational opportunities, including fellowship courses and the establishment of a Brachytherapy Society [66]. A more recent study in Australia and New Zealand echoes their concerns, highlighting the limited brachytherapy training available to radiation oncologists across their nations [67] whilst these issues have also been identified for trainee medical physicists [68]. Evidencing the need to address these concerns is challenging without a clear understanding of expected and observed demand. Furthermore, there is a cost implication of these training courses. Building on collaborations, both with and between jurisdictions, to support training in brachytherapy may help to mitigate these concerns.

The challenges of ensuring adequate training for the brachytherapy workforce will expand as the number of brachytherapy indications increases. Increasing evidence supports the use of brachytherapy for organ preservation in rectal cancer and for palliation in oesophageal cancer, whilst its use in head and neck cancers and ocular disease can also deliver preservation of function [69-71]. Access in these settings is, however, very variable and often limited irrespective of health jurisdiction [72]. This may in part reflect limitations of the evidence base. For example, in rectal cancer the role of brachytherapy has historically been limited to patients where frailty or co-morbidity prevents resection. However, as the wider role of radiotherapy in organ preservation gains greater evidence and the demographics of an aging population impact services, the role of brachytherapy in rectal cancer may well increase [73]. Understanding the demand for these less frequent indications will be crucial to ensuring equity of access.

It is clear that further health services research is required to reduce the uncertainties that may limit investment in brachytherapy and better inform workforce planning. In the first instance, modelling of the optimal utilisation rate across jurisdictions should be considered to determine population level need now and in the future. These should incorporate a range of "acceptable" levels of utilisation, particularly for novel indications and in diagnoses where uncertainty exists, to enable recognition of preference sensitive care. Extending beyond this, and in line with the Brachy-HERO project, there is then a need to understand how brachytherapy is used currently. Existing routine datasets maybe used where available, supplemented by prospective audits and clinician surveys, as are underway currently (personal communication with Peter Niehoff). The challenges to capturing these data are even greater in low and low-middle income countries where the burden of disease is considerably larger [74, 75]. Strengthening the existing networks of brachytherapy professionals both nationally and internationally is urgently required to support this work in addition to addressing the training requirements mentioned previously [66].

Beyond this, where observed utilisation is found to fall short of optimal utilisation, there is a need to determine which diagnoses are driving this discrepancy and consider qualitative studies to better understand its causes. Integrating the optimal BTU models, with observed utilisation rates and greater understanding of the causes of any discrepancy can then deliver clear understanding of the extent to which further investment in brachytherapy may improve utilisation and indeed, consider how utilisation may be expected to change over time with varying cancer incidence patterns. By supplementing these analyses with jurisdiction specific TD-ABC studies it is then possible to deliver a detailed understanding of the workforce and finance required to increase brachytherapy utilisation to an acceptable level. For new indications, the costs derived from these studies, combined with randomised data, can then inform cost-effectiveness analyses, providing decision-makers with the necessary information to determine the appropriateness of further investment.

Conclusion

Health services research can help to identify the expected level of need for brachytherapy, enable comparisons with existing utilisation and inform the costs and cost-effectiveness of aligning utilisation to modelled demand. In all of these areas, work in brachytherapy lags behind that in EBRT. Further work is urgently needed to redress this balance and ensure greater availability of BT where appropriate.

1. References

1. The Lancet, O., *Brachytherapy-a dose of pragmatism needed.* Lancet Oncol, 2021. **22**(6): p. 737 DOI: 10.1016/s1470-2045(21)00299-0.
2. GEC-ESTRO, *The GEC-ESTRO Handbook of Brachytherapy*. 2019.
3. Oncology, N.C.G.i. *Cervical Cancer*. 2021; Available from: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
4. Oncology, N.C.G.i. *Uterine Cancer*. 2022; Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
5. NCCN. *NCCN guideline: Prostate Cancer*. 2022; Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459.
6. Small, W., Jr., et al., *American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy.* Brachytherapy, 2012. **11**(1): p. 58-67 DOI: 10.1016/j.brachy.2011.08.005.
7. Viswanathan, A.N., et al., *American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy.* Brachytherapy, 2012. **11**(1): p. 47-52 DOI: 10.1016/j.brachy.2011.07.002.
8. Yamada, Y., et al., *American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy.* Brachytherapy, 2012. **11**(1): p. 20-32 DOI: 10.1016/j.brachy.2011.09.008.
9. Davis, B.J., et al., *American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy.* Brachytherapy, 2012. **11**(1): p. 6-19.
10. Holschneider, C.H., et al., *Brachytherapy: A critical component of primary radiation therapy for cervical cancer: From the Society of Gynecologic Oncology (SGO) and the American Brachytherapy Society (ABS).* Brachytherapy, 2019. **18**(2): p. 123-132 DOI: 10.1016/j.brachy.2018.11.009.
11. NSW, e.C.I. *Gynaecological Malignancies*. 2022; Available from: https://www.eviq.org.au/radiation-oncology/gynaecological.
12. NSW, e.C.I. *Prostate Cancer*. 2016; Available from: https://www.eviq.org.au/radiation-oncology/urogenital/prostate.
13. Han, K., et al., *Trends in the utilization of brachytherapy in cervical cancer in the United States.* International Journal of Radiation Oncology* Biology* Physics, 2013. **87**(1): p. 111-119 DOI: 10.1016/j.ijrobp.2013.05.033.
14. Lanciano, R.M., et al., *Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies.* International Journal of Radiation Oncology* Biology* Physics, 1991. **20**(4): p. 667-676 DOI: 10.1016/0360-3016(91)90007-q.
15. Robin, T.P., et al., *Disparities in standard of care treatment and associated survival decrement in patients with locally advanced cervical cancer.* Gynecologic oncology, 2016. **143**(2): p. 319-325 DOI: 10.1016/j.ygyno.2016.09.009.
16. Wortman, B., et al., *Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy.* British journal of cancer, 2018. **119**(9): p. 1067-1074.
17. Colombo, N., et al., *ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up.* International Journal of Gynecologic Cancer, 2016. **26**(1).

18. Meyer, L.A., 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.* Journal of Clinical Oncology, 2015. **33**(26): p. 2908-2913 DOI: 10.1200/JCO.2015.62.5459.
19. Chargari, C., et al., *Brachytherapy: An overview for clinicians.* CA: a cancer journal for clinicians, 2019. **69**(5): p. 386-401 DOI: 10.3322/caac.21578.
20. Gill, B.S., et al., *National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements.* International Journal of Radiation Oncology* Biology* Physics, 2014. **90**(5): p. 1083-1090 DOI: 10.1016/j.ijrobp.2014.07.017.
21. Nout, R.A., et al., *Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial.* The Lancet, 2010. **375**(9717): p. 816-823 DOI: https://doi.org/10.1016/S0140-6736(09)62163-2.
22. Morris, W.J., et al., *Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer.* Int J Radiat Oncol Biol Phys, 2017. **98**(2): p. 275-285 DOI: 10.1016/j.ijrobp.2016.11.026.
23. Hoskin, P.J., et al., *Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer.* Radiotherapy and Oncology, 2012. **103**(2): p. 217-222.
24. Hoskin, P.J., et al., *Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results.* Radiotherapy and Oncology, 2021. **154**: p. 214-219 DOI: 10.1016/j.radonc.2020.09.047.
25. Grimm, P., et al., *Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group.* BJU international, 2012. **109**: p. 22-29 DOI: 10.1111/j.1464-410X.2011.10827.x.
26. Bolla, M., et al., *Short androgen suppression and radiation dose escalation for intermediate-and high-risk localized prostate cancer: results of EORTC trial 22991.* Journal of Clinical Oncology, 2016. **34**(15): p. 1748-1756 DOI: 10.1200/JCO.2015.64.8055.
27. Bolla, M., et al., *Short androgen suppression and radiation dose escalation in prostate cancer: 12-year results of EORTC trial 22991 in patients with localized intermediate-risk disease.* Journal of Clinical Oncology, 2021. **39**(27): p. 3022-3033 DOI: 10.1200/JCO.21.00855.
28. Thompson, S., et al., *Estimation of the optimal brachytherapy utilization rate in the treatment of carcinoma of the uterine cervix: review of clinical practice guidelines and primary evidence.* Cancer, 2006. **107**(12): p. 2932-2941 DOI: 10.1002/cncr.22337.
29. Thompson, S.R., et al., *Estimation of optimal brachytherapy utilization rate in the treatment of malignancies of the uterine corpus by a review of clinical practice guidelines and the primary evidence.* International Journal of Radiation Oncology* Biology* Physics, 2008. **72**(3): p. 849-858 DOI: 10.1016/j.ijrobp.2008.01.022.

30. Thompson, S.R., et al., *Estimation of the optimal utilisation rates of radical prostatectomy, external beam radiotherapy and brachytherapy in the treatment of prostate cancer by a review of clinical practice guidelines.* Radiotherapy and Oncology, 2016. **118**(1): p. 118-121 DOI: 10.1016/j.radonc.2015.12.023.
31. Chopra, S., et al., *External radiation and brachytherapy resource deficit for cervical cancer in India: call to action for treatment of all.* Journal of global oncology, 2019. **5**.
32. Borras, J.M., et al., *The optimal utilization proportion of external beam radiotherapy in European countries: An ESTRO-HERO analysis.* Radiotherapy and Oncology, 2015. **116**(1): p. 38-44 DOI: 10.1016/j.radonc.2015.04.018.
33. Borras, J.M., *SP-0124: Optimal utilisation of brachytherapy in Europecan it be measured?* Radiotherapy and Oncology, 2017. **123**: p. S57 DOI: 10.1016/S0167-8140(17)30566-2.
34. Hanna, S.A., et al., *Lessons from the Brazilian radiotherapy expansion plan: A project database study.* The Lancet Regional Health-Americas, 2022. **14**: p. 100333.
35. Rodin, D., et al., *Scale-up of radiotherapy for cervical cancer in the era of human papillomavirus vaccination in low-income and middle-income countries: a model-based analysis of need and economic impact.* The lancet oncology, 2019. **20**(7): p. 915-923 DOI: 10.1016/S1470-2045(19)30308-0.
36. Guedea, F., et al., *Brachytherapy in the United Kingdom and Spain: a subset analysis of a European pattern of care survey.* Clinical and Translational Oncology, 2009. **11**(8): p. 534-538 DOI: 10.1007/s12094-009-0398-7.
37. Salembier, C., et al., *Brachytherapy in Belgium in 2018. A national survey of the brachytherapy study group of the Belgian SocieTy for Radiotherapy and Oncology (BeSTRO).* Radiother Oncol, 2020. **150**: p. 245-252 DOI: 10.1016/j.radonc.2020.07.010.
38. Glaser, S., et al., *Brachytherapy boost for prostate cancer: trends in care and survival outcomes.* Brachytherapy, 2017. **16**(2): p. 330-341 DOI: 10.1016/j.brachy.2016.12.015.
39. Orio III, P.F., et al., *The decreased use of brachytherapy boost for intermediate and high-risk prostate cancer despite evidence supporting its effectiveness.* Brachytherapy, 2016. **15**(6): p. 701-706.
40. Lecavalier-Barsoum, M., et al., *Utilization of brachytherapy in Quebec, Canada.* Brachytherapy, 2021. **20**(6): p. 1282-1288 DOI: https://doi.org/10.1016/j.brachy.2021.07.002.
41. Kim, Y.A., et al., *Brachytherapy utilization rate and effect on survival in cervical cancer patients in Korea.* J Gynecol Oncol, 2021. **32**(6): p. e85 DOI: 10.3802/jgo.2021.32.e85.
42. Morris, S., et al., *Economic analysis in healthcare*. 2012: John Wiley & Sons.
43. Danzon, P.M., et al., *Objectives, budgets, thresholds, and opportunity costs—a health economics approach: an ISPOR Special Task Force report [4].* Value in Health, 2018. **21**(2): p. 140-145 DOI: 10.1016/j.jval.2017.12.008.
44. Amin, N.P., D.J. Sher, and A.A. Konski, *Systematic review of the cost effectiveness of radiation therapy for prostate cancer from 2003 to 2013.* Applied health economics and health policy, 2014. **12**(4): p. 391-408 DOI: 10.1007/s40258-014-0106-9.
45. Lievens, Y., et al., *How public health services pay for radiotherapy in Europe: an ESTRO–HERO analysis of reimbursement.* The Lancet Oncology, 2020. **21**(1): p. e42-e54.

46. Vu, C.C., M.S. Jawad, and D.J. Krauss. *The cost-effectiveness and value proposition of brachytherapy*. in *Seminars in radiation oncology*. 2020. Elsevier.
47. Defourny, N., et al., *Cost evaluations of radiotherapy: what do we know? An ESTRO-HERO analysis.* Radiotherapy and Oncology, 2016. **121**(3): p. 468-474.
48. Defourny, N., et al., *National costs and resource requirements of external beam radiotherapy: A time-driven activity-based costing model from the ESTRO-HERO project.* Radiotherapy and Oncology, 2019. **138**: p. 187-194 DOI: 10.1016/j.radonc.2019.06.015.
49. Kaplan, R.S. and M.E. Porter, *How to solve the cost crisis in health care.* Harv Bus Rev, 2011. **89**(9): p. 46-52.
50. Schutzer, M.E., D.W. Arthur, and M.S. Anscher, *Time-driven activity-based costing: a comparative cost analysis of whole-breast radiotherapy versus balloon-based brachytherapy in the management of early-stage breast cancer.* Journal of oncology practice, 2016. **12**(5): p. e584-e593 DOI: 10.1200/JOP.2015.008441.
51. Ilg, A.M., et al., *Time-driven activity-based costing of low-dose-rate and high-dose-rate brachytherapy for low-risk prostate cancer.* Brachytherapy, 2016. **15**(6): p. 760-767 DOI: 10.1016/j.brachy.2016.08.008.
52. Dziemianowicz, M., J. Burmeister, and M. Dominello, *Examining the financial impact of altered fractionation in breast cancer: an analysis using time-driven activity-based costing.* Practical Radiation Oncology, 2021. **11**(4): p. 245-251 DOI: 10.1016/j.prro.2021.01.003.
53. Bonastre, J., et al., *Implications of learning effects for hospital costs of new health technologies: the case of intensity modulated radiation therapy.* Int J Technol Assess Health Care, 2007. **23**(2): p. 248-54 DOI: 10.1017/s026646230707033x.
54. Durkee, B.Y. and M.K. Buyyounouski, *The case for prostate brachytherapy in the Affordable Care Act era.* International Journal of Radiation Oncology, Biology, Physics, 2015. **91**(3): p. 465-467 DOI: 10.1016/j.ijrobp.2014.10.014.
55. Rao, C., et al., *A cost-effectiveness analysis of contact x-ray brachytherapy for the treatment of patients with rectal cancer following a partial response to chemoradiotherapy.* Clinical Oncology, 2018. **30**(3): p. 166-177 DOI: 10.1016/j.clon.2017.11.015.
56. Vaidya, A., et al., *Health economics of targeted intraoperative radiotherapy (TARGIT-IORT) for early breast cancer: a cost-effectiveness analysis in the United Kingdom.* BMJ open, 2017. **7**(8): p. e014944 DOI: 10.1136/bmjopen-2016-014944.
57. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force.* Value Health, 2013. **16**(2): p. 231-50 DOI: 10.1016/j.jval.2013.02.002.
58. Becerra, V., et al., *Economic evaluation of treatments for patients with localized prostate cancer in Europe: a systematic review.* BMC health services research, 2016. **16**(1): p. 1-13 DOI: 10.1186/s12913-016-1781-z.
59. Gray, C. and K. Campbell, *High dose rate brachytherapy versus low dose rate brachytherapy for the treatment of prostate cancer: A review of clinical effectiveness and cost-effectiveness.* 2019.
60. Muralidhar, V. and P.L. Nguyen. *Maximizing resources in the local treatment of prostate cancer: A summary of cost-effectiveness studies*. in *Urologic Oncology: Seminars and Original Investigations*. 2017. Elsevier.

61. Sharma, D., et al., *National Healthcare Economic Evaluation Guidelines: A Cross-Country Comparison.* Pharmacoecon Open, 2021. **5**(3): p. 349-364 DOI: 10.1007/s41669-020-00250-7.
62. Mailhot Vega, R.B., Jr., et al., *Cost in perspective: direct assessment of American market acceptability of Co-60 in gynecologic high-dose-rate brachytherapy and contrast with experience abroad.* J Contemp Brachytherapy, 2018. **10**(6): p. 503-509 DOI: 10.5114/jcb.2018.79928.
63. Spencer, K., et al., *Variable and fixed costs in NHS radiotherapy; consequences for increasing hypo fractionation.* Radiotherapy and Oncology, 2022. **166**: p. 180-188 DOI: 10.1016/j.radonc.2021.11.035.
64. McGuffin, M., et al., *Who should bear the cost of convenience? A cost-effectiveness analysis comparing external beam and brachytherapy radiotherapy techniques for early stage breast cancer.* Clinical Oncology, 2017. **29**(3): p. e57-e63.
65. National Institute for Health and Care Excellence (NICE), U. *NICE health technology evaluations: the manual*. 2022; Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741.
66. Banerjee, S., U. Mahantshetty, and S. Shrivastava, *Brachytherapy in India–a long road ahead.* Journal of Contemporary Brachytherapy, 2014. **6**(3): p. 331-335 DOI: 10.5114/jcb.2014.45761.
67. Ong, W.L., et al., *Survey of brachytherapy training experience among radiation oncology trainees and fellows in the Royal Australian and New Zealand College of Radiologists (RANZCR).* Journal of Medical Imaging and Radiation Oncology, 2022.
68. Haworth, A., *Brachytherapy: a dying art or missed opportunity?* Australasian Physical & Engineering Sciences in Medicine, 2016. **39**(1): p. 5-9 DOI: 10.1007/s13246-016-0430-5.
69. Homs, M.Y., et al., *Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial.* Lancet, 2004. **364**(9444): p. 1497-504 DOI: 10.1016/s0140-6736(04)17272-3.
70. Bhalavat, R., et al., *High-dose-rate interstitial brachytherapy in head and neck cancer: do we need a look back into a forgotten art - a single institute experience.* J Contemp Brachytherapy, 2017. **9**(2): p. 124-131 DOI: 10.5114/jcb.2017.67147.
71. Rodin, J., 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): p. 454-462 DOI: 10.5114/jcb.2018.79399.
72. Adamson, D., et al., *Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial.* The Lancet Gastroenterology & Hepatology, 2021. **6**(4): p. 292-303 DOI: https://doi.org/10.1016/S2468-1253(21)00004-2.
73. Gérard, J.-P., et al., *Planned organ preservation for early T2-3 rectal adenocarcinoma: A French, multicentre study.* European Journal of Cancer, 2019. **108**: p. 1-16 DOI: https://doi.org/10.1016/j.ejca.2018.11.022.
74. Ngwa, W., et al., *Cancer in sub-Saharan Africa: a Lancet Oncology Commission.* Lancet Oncol, 2022. **23**(6): p. e251-e312 DOI: 10.1016/s1470-2045(21)00720-8.
75. Sinha, S., et al., *Adopting Health Economic Research in Radiation Oncology: A Perspective From Low- or Middle-Income Countries.* JCO Glob Oncol, 2022. **8**: p. e2100374 DOI: 10.1200/go.21.00374.