Technical Innovations & Patient Support in Radiation Oncology 16 (2020) 39–47

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.elsevier.com/locate/tipsro

Review article

Practical brachytherapy solutions to an age-old quandary

N. Thiruthaneeswaran [a,b,*], H. Tharmalingam [c], P.J. Hoskin [a,c]

[a] Division of Cancer Sciences, The University of Manchester, Manchester, UK
[b] Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia
[c] Mount Vernon Cancer Centre, Northwood, UK

ARTICLE INFO

Article history:
Received 5 July 2020
Received in revised form 17 September 2020
Accepted 18 September 2020
Available online 26 October 2020

Keywords:
Brachytherapy
High dose-rate (HDR)
Geriatric oncology
Elderly
Radiotherapy

ABSTRACT

Cancer is predominantly a disease of the elderly and as population life expectancy increases, so will the incidence of malignant disease. Elderly patients often have other comorbidities and social complexities, increasing the support required to safely deliver all treatment modalities. Brachytherapy is a relatively simple technique by which radiation therapy can be delivered. It offers dosimetric advantages through a highly conformal dose distribution thereby limiting radiation exposure to normal tissues reducing toxicity. Requiring fewer hospital visits, it also offers practical and logistical advantages to the elderly population and in many cases can be performed without the need for general anaesthesia. In tumour streams where brachytherapy forms part of the curative management, it should not be omitted in elderly patients who are medically fit for treatment. In the palliative setting, brachytherapy often offers an excellent means for achieving either local tumour and/or symptom control and should be actively considered in the therapeutic armamentarium of the oncologist in this context.

Introduction

The World Health Organisation forecasts a doubling of the current population aged above 60 by 2050 meaning this cohort will make up 22% of the total global populace [1]. Concurrently, the burden of cancer in the ageing population has increased considerably and will continue to do so in the future posing a unique global healthcare challenge [2,3]. With increasing life expectancy and delayed presentation and diagnosis, due in part to cancer screening ineligibility, older patients with locally advanced disease will represent a greater proportion of patients seen in cancer clinics. There is no universally accepted definition of elderly. It ranges from a chronological time point of 65 years, biologically a deterioration of physiological functions and in some societies as the point when active contribution is no longer possible [4]. Older cancer patients are a heterogeneous group and concerted efforts need to be made by treating specialists such that the treatment decision process is not affected by unconscious bias as a function of chronological age [5]. Due to constraints within the current health care infrastructure appropriate assessment of the elderly patients with respect to frailty, comorbidities and psychosocial support is often inadequate [6–8]. In situations where a formal geriatric assessment is not available, short assessment tools may aid with fitness for treatment decisions but are still not in widespread use [9].

Radiotherapy has been the cornerstone of treatment in frail patients when surgery has been excluded but often a palliative approach is adopted over a curative one due to perceived intolerance of toxicity, despite a paucity of clinical trial data to support this. Whilst advances in the precision of external bean radiotherapy (EBRT) techniques minimise toxicities reported in earlier clinical trials, alternative treatment options such as brachytherapy may provide distinct advantages in this patient cohort. Consensus guidelines from the International Geriatric Radiotherapy Group have recognised brachytherapy as an ideal therapeutic modality in some circumstances but the radiotherapy task force of the International Society of Geriatric Oncology (SIOG) recommendations are more limiting [10,11]. Brachytherapy is a highly conformal treatment method designed to deliver radiation by placing radioactive sources close to or within a tumour. It takes advantage of one of the most fundamental principles of radiation physics (inverse square law) with distinct radiobiological advantages. The dose exponentially decreases with distance away from the source creating a very sharp drop-off hence either limiting or completely sparing the adjacent normal tissues from exposure to radiation. Brachytherapy can be interstitial with permanent radioactive seeds (low dose rate, LDR) or more commonly via a catheter delivery sys-

* Corresponding author at: Division of Cancer Sciences, The University of Manchester, Manchester, UK.
E-mail address: nilujat@ausdoctors.net (N. Thiruthaneeswaran).

https://doi.org/10.1016/j.tipsro.2020.09.004

Table 1
Phase II/III trials and key retrospective studies of brachytherapy in the elderly.

Tumour site	Study	Design	N	Median age (range)	Stage	Brachytherapy^	Visits[β]	EBRT	Median F/U (months)	Outcome	Toxicity
Gynecological	Kobayashi (2014) [22]	Case series (cervix)	105	77 (70–89)	Ib-IVa	6 Gy × 4	4–5	50 Gy/25–28 #	59	5 yr CSS 78%	GI ≥ Gr 3 2%; GU 4.2%
	Coon (2008) [75]	Case series (endometrial)	49	65 (31–91)	I-III	4 Gy × 5 (if EBRT given) or 7 Gy × 5 bid	In-pt	45–50 Gy/20–25#	33	3 yr CSS 93% & OS 83%	4/49 had late ≥ Gr 2 GI
	Nout (2010) [26] PORTEC-2	Phase III (endometrial)	427	70	1c – 2a	7 Gy × 3 HDR or 30 Gy LDR VBT	3	46 Gy/23# (control arm)	45	No diff in LRR or OS	significantly lower GI toxicity with VBT
Prostate	Satya (2005) [34]	Phase III	104	65 (49–74)	Int. & high risk	35 Gy over 48 hours LDR Ir^{192}	In-pt (2 days)	40 Gy/20# + boost vs. 66 Gy/33#	98	5-yr BRFS 71% vs 39%, p = 0.0024	GI ≥ G3 3.9% vs 1.9% NS GU ≥ G3 HR 13.7% vs 3.2% NS
	Hoskin (2012) [33]	Phase III	218	70 (47–80)	Int. & high risk	17 Gy/2# in 24hrs	In-pt (2 days)	35.75 Gy/13# + boost vs 55 Gy/20# EBRT prostate	85	7-yr BRFS 66% vs 48%, p = 0.04	Severe GI 7% vs 6% NS Severe GU 26% vs 26%
	Khor (2013) [76]	Matched case study	344	67 (51–77)	T1-T3b	6.5 Gy × 3	In-pt (2 days)	46 Gy/23# vs 74 gy/37#	60.5	5-yr BRFS 79.8 % vs 70.9%	Increased urethral stricture 0.3% vs 11.8%
	Morris (2016) [35]	Phase III	398	68 (45–86)	Int. & high risk	^{125}I LDR boost (115 Gy)	In-pt (2 days)	46 Gy/23# EBRT whole pelvis + 125I LDR boost (115 Gy) vs 46 Gy/23# EBRT whole pelvis + 32 Gy/16# EBRT prostate boost	78	9-yr BRFS 83% vs 62%, p < 0.001	GI ≥ G3 8.6% vs 2.2% NS GU ≥ G3 18.4% vs 5.2%, p < 0.001 Late catheterization 12% vs 3%, p < 0.001
	Yamazaki (2018) [77]	Case series (matched controls ≤ 75yrs)	241	77 (75–86)	All risk (85% int & high)	All BT options (LDR, HDR monotherapy)	2–9	74 Gy/37#	87	7 yr BRFS 94.9% elderly vs 96.4% younger (p = 0.6)	Similar GI and GU in aged matched
Rectum	Dizdarevic (2019) [38]	Ph II (definitive)	51	68 (61–77)	T2 or T3, N0-1	5 Gy (HDR) at 1 cm applicator surface single channel	EBRT = 6 weeks BT = 1 day	CTVp = 60 Gy/30# IMRT CTVn = 50 Gy/30# IMRT	60	LR 39% 11/52 salvage TME OS 85%	QoL score did not differ between baseline
	Rijkmans (2017) [39] HERBERT Dose-esca-lation	Ph I (definitive)	38	83 (57–94)	T2-4 N0-1	5–8 Gy × 3 (HDR) at 2 cm applicator surface multi-channel DLT ≥ 3 Gy proctitis < 6 weeks after HDREBT	EBRT = 13 days BT = 3 days	39 Gy/13# EBRT (4/wk)	24	Recommended dose = 7 Gy per HDR # L-PFS = 42% OS = 63%	10 pts ≥ 3Gr late toxicity (1 = Gr 4)
	Appelt (2015) [41]	Ph III (neo-adjuvant)	221	63 (35–78)	T3-4 N0-2 M0	5 Gy × 2 (HDR) 1 cm applicator surface single channel	EBRT = 28 days BT = 2 days (incorporated)	50.4 Gy/28# (5#/week)	65	No difference in R0 resection PFS 63.9% vs 52.0%, (HR = 1.22, p = 0.32) OS 70.6% vs 63.6%, (HR = 1.24, p = 0.34)	no difference in the prevalence of stoma
	Corner (2010) [40]	Case series (definitive & palliative)	70 (52 definitive RT)	82 (33–97)	≥T2	6 Gy × 6 (HDR) monotherapy or 6 Gy × 2 (HDR) adjuvant 1 cm applicator surface single channel	Varied	45 Gy/25# in 36 pts	NR	Complete response 58%; partial >50% response 27%	6 pts late toxicity

Table 1 (*continued*)

Tumour site	Study	Design	N	Median age (range)	Stage	Brachytherapy^	Visits[β]	EBRT	Median F/U (months)	Outcome	Toxicity
	Vuong (2007) [42]	Ph II (neo-adjuvant)	100	N/R	T2-4, N0-1	6.5 Gy × 4 (HDR) 1 cm applicator surface single channel??	4 days	N/A	60	DFS 65% OS 70% 21pt had post –operative EBRT for pN1	postoperative leak rate of 9% (5/45) abdominoperineal resection rate was 53% (51/96) and the sphincter preservation rate was 47% (45/96)
Oesophagus	Sur (2002) [78]	Phase III Multicentre (palliative)	232	56.8	All stages	8 Gy × 2 vs. 6 Gy × 3 at 1 cm source axis single channel (under sedation)	2–3	N/A	8	No difference between study groups	25 pts fibrotic strictures. Similar in both groups (p > 0.05)
	Homs (2004) [79]	Phase III multicentre (palliative) Stent vs BT	209	69	All stages	12 Gy × 1 at 1 cm applicator surface single channel (under sedation)	1	N/A	1	long-term relief of dysphagia was better after BT	Stent vs. BT (33%) vs (21%); p = 0·02)
	Bergquist (2005) [80]	Phase III (palliative) Stent vs BT	65	72 (60–82	All stages	7 Gy × 3 at 1 cm applicator surface single channel (under sedation)	3	N/A	3	Delayed with BT (1mo vs 3 mo) OS equivalent	No difference in toxicity.
	Rosenblatt (2010) [47]	Phase III (international, palliative) BT + EBRT vs. BT	219	61.3 (15–102)	All stages	8 Gy × 2 at 1 cm applicator surface single channel	2	30 Gy/10# daily (Arm A)	6.5	DRE absolute benefit of + 18% at 200 days (p = 0.019). No difference in OS.	No difference in toxicity. 21/109 pts crossed over
	Amdal (2013) [81]	Phase III (palliative) Stent + BT vs stent	41	71 (47–91)	T4No, TxN1, M1	8 Gy × 3 at 0.7 cm applicator surface single channel (under sedation)	3	N/A	1.2	At 3 wks improved dysphagia with stent + BT (p = 0.02); no difference at 7 wks	Stent complication and prolonged hospital stay in stent + BT; no sig toxicity in BT alone
	Zhu (2014) [82]	Phase III multicentre (palliative) I^{135}stent vs stent	160	71 (60–79)	All stages	stent loaded with ^{125}iodine radioactive seeds	Min 3 day stay	N/A	4.6	1 mo improved OS (p = 0.005)	No difference in complication 1pt with oesophagotracheal fistula
	Aggarwal (2015) [48]	Retrospective (inoperable & palliative)	59	77 (53–88)	All stages	15 Gy (range 10–31 Gy) 1 at 1 cm applicator surface single channel	1–5	30 Gy/10# daily or 4.5 Gy × 6/1# per week	28	89% improved dysphagia score. OS of all pts was 12.3 months; 1, 2 and 3 yr rates were 51, 19 & 7%.	1pt oesophageal ulceration; 12 pts repeat endoscopy for symptoms post BT
	Sharma (2002) [83]	Retrospective	58	64 (32–88)	IV	6 Gy × 2 at 1 cm applicator surface single channel	2	20 Gy/5# or 30 Gy/10#		Median dysphagia-free survival 10 months.	Stricture 9 (15%), ulceration in 6 (10%), fistula in 3 patients (5%).
LUNG	Stout (2000) [84]	Phase III (palliative)	99	68 (40–84)	IV	15 Gy × 1 at 1 cm applicator surface single channel	1	30 Gy/8# (control arm)	NR	Improved dysphagia (85 vs. 45% P = 0.00085) Better global palliation with EBRT 59 vs. 83% P = 0.029	No difference in toxicity
	Langendijk (2001) [53]	Phase III (palliative)	95	67	IIIB tumour in main or lobar bronchus	7.5 Gy × 2 at 1 cm applicator surface single channel (alone vs + EBRT)	2	Radical EBRT (60 Gy) or palliative EBRT (30 Gy)	NR	Improved dyspnea over time (P = 0.02) for main bronchus tumour. No diff OS	2 pts with fistula in combination treatment

(*continued on next page*)

Table 1 (*continued*)

Tumour site	Study	Design	N	Median age (range)	Stage	Brachytherapy^	Visits[β]	EBRT	Median F/U (months)	Outcome	Toxicity
	Mallick (2006) [85]	Phase III (palliative)	45	65 (35–75)		8 Gy × 2 vs. 10 Gy × 1 vs 15 Gy × 1 at 1 cm	1–2	30 Gy/10 # (arm A & B)	6	No difference between arms	No difference in toxicity
	Niemoeller (2013) [86]	Phase III (palliative)	142	65 (39–88)	All stages	3.8 Gy × 4 vs. 7.2 Gy × 2 at 1 cm	2–4	N/A	4	Improved LRR with 2# 11wk vs. 27 (p = 0.015)	No difference in toxicity
Breast	Strnad (2016) [55]	Phase III	1184	62 (54–68)	pT1–2a (<3 cm) pN0/Nmi	4·0 Gy × 8 or 4.3 × 7 Gy HDR 50 Gy with pulses of 0·60–0·80 Gy/h PDR	1–8	50·0–50·4 Gy/25–28# (control arm)	79	No difference in LRR or OS	No difference in toxicity
	Hannoun-Lévi (2020) [56]	Phase I/II	26	77 (69–89)	pT ≤ 2 cm	16 Gy × 1	2	N/A	63	5-yr LRFS 100%, MFS 95.5%, & OS 88.5%	5 pts late toxicity < Gr 3

BT = brachytherapy; TME = total mesorectal excision; DLT = dose limiting toxicity; DRE = dysphagia relief experience; β = number of hospital visits for brachytherapy, NR = not reported; OS = overall survival; NR = not reported; LRR = local recurrence rate; EBRT = external beam radiotherapy; HDR = high dose rate; PDR = pulsed dose rate; LDR = low dose rate; MFS = metastatic free survival; ^ Ir^{192} unless stated otherwise; GI = gastrointestinal; GU = genitourinary.

tem for a temporary radioactive source (high dose rate, HDR or pulse dose rate, PDR). Unlike LDR seed brachytherapy, HDR planning is prospective with target coverage defined prior to treatment, allowing for plan optimization. Additional advantages of brachytherapy over EBRT are minimal inter and intra-fraction motion and improved tumour dose painting, with the main disadvantage to the patient being that it is an invasive procedure.

Despite limitations relating to a shortfall in training and experience for radiation oncologists, the availability of equipment and support in many institutions, the technique itself is rather simple and studies report few serious complications. Practical advantages of brachytherapy include short duration of treatment and in-patient hospital stay which may be preferential for elderly patients compared to a protracted course of treatment requiring daily commutes. Although general or spinal anaesthesia is required for interstitial implants, this alone should not deter clinicians from offering treatment, particularly where brachytherapy forms part of the curative management of tumours. Aside from the appropriate selection of patients through formal assessments, alternative methods using regional or local anaesthesia should also be explored.

Financial hurdles are often cited as barriers to brachytherapy. The upfront cost of setting up of a service coupled with lower reimbursement in some countries can make it an unattractive choice despite associations with improved survival [12]. In addition, the perceived workflow of brachytherapy compared to EBRT would require a radiation oncologist to dedicate a fixed time of 0.5–2 hours per patient versus shorter intervals over a period of 1–2 months for EBRT to include on-treatment review. Overall the clinician time per patient is likely to be less with brachytherapy [13]. Moreover, cost effective analysis is specific to each health care setting and conflicting depending on the model used. Comparison of costs in the USA for prostate treatment showed brachytherapy ($17 183) to be more cost-effective than SBRT ($27 145), IMRT ($37 090) and protons ($54 706), the latter of which is being delivered with a less robust evidence base [13,14]. In the UK, for high risk prostate cancer, a brachytherapy boost in combination with EBRT was found to deliver higher quality adjusted life years (8.82 vs 8.70) although at a slightly higher cost (£8591 vs £8225) compared to EBRT alone [15]. Similar cost-effectiveness has been reported for gynaecological malignancies and so citing financial toxicity as a barrier to brachytherapy is not credible [16,17].

This review summarises the evidence for brachytherapy in common malignancies affecting the elderly population, highlighting and questioning its underutilisation based on clinical outcomes and toxicity profiles in this age group both in the definitive and palliative setting. The focus will be on the most common malignancies in the elderly where radiotherapy is indicated; lung, breast, prostate, rectum and corpus uteri whilst recognising that brachytherapy can also be applied to a wider range of tumour sites such as skin, head and neck, liver and connective tissue cancers.

Search strategy

A literature search was used to examine relevant English language publications from PubMed supplemented by hand-searching of abstracts from recent international meetings. Key words used include ‘‘brachytherapy”, ‘‘elderly” ‘‘geriatric”, and ‘‘palliative” excluding reviews, editorials and commentaries from January 2000 to June 2020. Additional publications were identified by scanning references. Studies relevant to common solid tumours in the elderly population where brachytherapy may be indicated were identified. Studies using contact X-ray and where the median age was <60 for curative intent treatment were excluded. Table 1

summarises the brachytherapy studies pertinent to the elderly population.

Gynaecological cancer

The underutilisation of brachytherapy in locally advanced cervical cancer globally is widely recognised and this effect is more pronounced in the elderly population with studies from North America reporting 20% of women between ages 70–79 and up to 60% of women >80 years old not receiving brachytherapy [18,19]. Analysis of the cooperative oncology group studies (COG) clinical trials consisting of the largest stage IVA patient populations in the literature reported, brachytherapy was not completed in 35% of patients ≥70 years versus 13% of patients <40 and this is despite the fact that these clinical trials are undertaken at large tertiary centres where brachytherapy programmes are well established [20]. By contrast, neither the chemotherapy dose, number of chemotherapy cycles delivered nor the overall radiation treatment time were compromised due to increasing age [20]. Where poor renal function and cardiac comorbidities preclude concurrent chemotherapy, patients are often treated with EBRT alone without consideration of the brachytherapy boost. Medical comorbidities and anaesthetic risk are often cited as reasons for omission, however no formal anaesthetic risk assessments were conducted in these clinical trials. In addition, cervical brachytherapy procedures can be undertaken under regional or local anaesthesia and the number of fractionations and the treatment workflow can be tailored to the patient to maximise comfort [21]. A retrospective cohort series specifically addressing the impact of CT-based brachytherapy in 105 elderly patients (70–89 years) reported 5-year local control and cancer specific survival rates of 89% and 78% respectively with comparable toxicity profile to younger cohorts [22]. Brachytherapy is an essential component of cervical cancer (>Stage IB) and should not be omitted in elderly patients unless medically unsuitable. Unlike other solid tumours where brachytherapy is an alternate option, in cervical cancer it is a mandatory component of curative intent treatment and should not be substituted with EBRT or SBRT boosts which have poorer outcomes [23].

The peak age of endometrial cancer in the UK is 75–79 years with 27% of new cases in >75 years. In recent years the PORTEC and GOG trials have shaped practice in the post-operative setting in which almost half of the patients were >70 years old [24-26]. It was also this age group (≥70 years old) that had the highest rate of local recurrences in both trials. Vaginal vault brachytherapy (VBT) in the adjuvant setting is a practical method of treatment with minimal toxicity and well tolerated by older patients which if indicated should be offered. A retrospective review of patients ≥70 years found that FIGO stage and higher age resulted in less aggressive treatment being offered. Comorbidity on the other hand did not influence treatment choice highlighting the apparent discrepancies in the basis of oncological treatment decisions, particularly with respect to frailty, and the lack of evidence in the older age group [27]. The benefit of adjuvant chemotherapy combined with VBT for tumours with a high recurrence risk is unclear and the topic of ongoing trials. In the primary setting, brachytherapy either in combination with EBRT or in isolation using Heyman or Rotte applicators is effective for inoperable endometrial cancer [28,29] and this strategy should not be overlooked in elderly patients presenting with advanced stage disease.

Prostate cancer

Prostate cancer ranks as the second leading cause of death in men in developed countries. As life expectancy increases the diagnosis and management of prostate cancer in men >75 will represent an increasing challenge [30]. Radiotherapy trials that have informed best practice in prostate cancer have rarely included men greater than 80 years of age mainly due to the "watchful waiting" approach that is adopted in this age group [31]. In the curative setting, radiotherapy which can be EBRT, brachytherapy or SBRT is often the treatment of choice over surgery for elderly men with prostate cancer. Brachytherapy can be used in localised prostate cancer as a single modality treatment or as a boost in high risk localised disease. This is achieved with either permanent implant LDR radioactive seeds or HDR brachytherapy. Aside from the radiobiological gains of brachytherapy in a tumour with a relatively low alpha/beta ratio, it is also financially more viable both in set-up and maintenance than protracted courses of EBRT, particularly advantageous in low- and middle-income countries. Furthermore, it can significantly reduce the number of hospital visits, an additional benefit especially in the elderly population. In the setting of high-risk prostate cancer, fit elderly patients should be offered curative intent treatment. Despite the aforementioned advantages prostate brachytherapy is underutilised and this trend is pronounced in the elderly population [32]. Three randomised controlled trials (RCT) have shown significantly improve biochemical recurrence-free survival across all risk groups where a brachytherapy boost is delivered in combination with EBRT compared to EBRT alone, with no clinically significant difference in prevalence of late toxicity [33-35]. In carefully selected patients LDR seeds or two fraction HDR brachytherapy monotherapy has excellent local control rates even in high risk disease [36,37]. Salvage treatment for localised recurrence, although still in its infancy is being increasingly utilised in preference to prostatectomy with PSMA-PET imaging improving staging and patient selection, and the use of rectal spacer devices reducing rectal dose in the setting of re-irradiation. Brachytherapy is a safe, feasible and effective option for fit elderly men and should be considered following a formalised assessment for fitness and life expectancy.

Rectal cancer

Brachytherapy does not form part of the standard multimodal approach to rectal or anal cancer. However, organ preservation approaches to lower GI tumours have explored dose escalation with brachytherapy as an alternative to surgical management with encouraging results [38,39]. The main indication for brachytherapy in the elderly population with ano-rectal tumours is in those who are unfit for standard care with palliative options being offered for inoperable, locally advanced and recurrent disease. Endoluminal single or multi-channel applicators or alternative single line source catheters in the case of significant canal stenosis either alone or in combination with EBRT provides effective local control with rectal bleeding complete control in 65% of patients with 50% achieving complete pain control [40]. Palliative single dose (10 Gy) can be delivered to frail patients minimising hospital visits and the need for repeated treatments.

Pre-operative brachytherapy delivered in four fractions in a phase II trial resulted in pCR of 29% and DFS of 65%. However a RCT comparing preoperative CRT vs CRT plus HDR boost did not demonstrate a benefit of combination treatment although criticism is levelled at the relatively low HDR dose prescribed based on radiation dose response models in rectal cancer [41-43]. Despite the limitation in the early phase studies presented in Table 1, avoidance of colostomy with good sphincter preservation rate and local progression free survival makes this an extremely viable option for the older cohort of patients which ought to be considered. Given the major lifestyle challenges for elderly patients faced with a colostomy inclusion of the patient and their family with full presentation of the relative merits of different approaches is essential [44].

Oesophageal cancer

Annually 41% of all new oesophageal cancer cases in the UK are diagnosed in people aged ≥75 [45]. Intraluminal brachytherapy alone or in combination EBRT provides durable functional improvement in patients assessed to be unfit for curative intent treatment with surgery or combined modality treatment. A Cochrane systematic review on interventions for managing dysphagia reported that although self-expanding metallic stent (SEMS) provided immediate relief of symptoms combination of HDR brachytherapy with SEMS or EBRT reports a survival advantage, reduced requirement for re-interventions and possibly a better quality of life [46]. The largest RCT which compared HDR brachytherapy alone or in combination with EBRT demonstrated a significant benefit in the primary endpoint of dysphagia in favour of combination treatment, though no overall survival advantage [47]. Given the low median survival in the palliative setting promptly treating dysphagia through accessibility to brachytherapy ± SEMS can have a significant impact on QoL. The procedure is very feasible in the elderly population. It can be straightforward, quick, inexpensive and often performed without sedation using a nasogastric tube preloaded with an HDR after loading catheter and a single line source on an outpatient basis completed in a single visit in a couple of hours. [48,49]. An alternative method is a fluoroscopic/laparoscopic guided procedure combined with placement of SEMS, more suitable for multiple fractions. Currently there is no consensus on optimal treatment schedules but treatment protocols from RCT require 7–12 Gy/fraction in 1–3 fractions. Randomised trial toxicity data suggest brachytherapy is comparable to stent placement although a prolonged hospital stay in the stent group has been reported (Table 1). It is recommended that palliative oesophageal cases be discussed with a brachytherapist particularly if following comprehensive assessment, the life expectancy of the patient is >3 months when there is a clear advantage for brachytherapy with durable relief of dysphagia.

Lung cancer

Lung cancer is the most common cause of cancer mortality worldwide with incidence rates highest in people aged 85–89 [50]. Endobronchial brachytherapy (EBBT) alone or in combination may be used to palliate non-small cell lung cancers where bronchial obstruction or recurrence of central disease is evident. A Cochrane systematic review of EBBT compared to various treatment combinations including EBRT did not find an added benefit from brachytherapy although there was considerable heterogeneity between the studies [51]. The EORTC Elderly Task Force opinion paper has not addressed EBBT as a treatment option although there may be a subset of patients for example, those who have previously received EBRT and later present with obstructive symptoms, who would benefit from EBBT and in those it should be considered [52]. The failure in part to show a benefit over EBRT is due to the limited treated volume which encompasses a 2 cm diameter cylinder around the brachytherapy catheter and therefore does not address progression of untreated tumour outside the bronchus in the lung and mediastinum. EBRT is indicated in most cases because of extrabronchial bulky disease that cannot be addressed with EBBT. Patients with obstructing tumours in the main bronchus are those that are most likely to benefit with combination treatment [53].

Breast cancer

There is a strong correlation with increasing breast cancer risk and age with the peak prevalence of invasive disease occurring between 80 and 89 years. Adjuvant radiotherapy is the mainstay of breast conservation surgery. Recent randomised trials specific to the older population have addressed the omission of adjuvant radiotherapy in low risk older patients. The largest of these trials are Prime II and CALBG recruiting patients ≥65 years with low risk disease reporting no difference in overall survival in those with favourable tumour characteristics, however compliance to a minimum of 5 years of endocrine treatment is required [54]. Although practice is variable, older patients should be offered the option of omission of radiotherapy after breast conserving surgery for selected patients (i.e. T1N0, ER positive). For all other patients where radiotherapy is indicated, accelerated partial breast brachytherapy where catheters are placed intra-operatively and treatment delivered over a few days, is an alternative to whole breast EBRT. The most recent trial published demonstrates non-inferiority over whole breast EBRT and hence APBI can be added to the array of treatment options available [55]. Trials specific to the older population with single fraction APBI brachytherapy are underway with favourable early outcome [56]. Single fraction APBI may be particularly beneficial for older patients who are not close to a cancer centre, as well as reducing the total cost of treatment offering advantage over recently published five fraction schedules [57,58]. The challenge remains on how best to select patients as trials continue to further refine and provide biological rationale for selection through biomarker stratification.

Brachytherapy can also have an important role in local recurrence where surgery is not feasible and systemic options are limited. Interstitial or surface mould techniques can deliver localised high dose radiation to achieve good palliation of local pain and bleeding.

Other malignancies

Non-melanotic skin cancers (NMSC) have increased by 56% over the last decade with incidence rates highest in ≥90 years old and 47% of all new cases occurring in ≥75 years [59]. HDR brachytherapy for NMSC is a non-invasive procedure for tumours <0.5 cm thickness and on flat surfaces (up to 5 cm diameter), using surface applicators or custom moulds. Treatment schedules range from 5-12 fractions achieving biologically equivalent doses often exceeding 60–70 Gy. Treatment is well tolerated, with excellent local control (98%) and cosmesis [60,61]. Tumours >0.5 cm thickness and located on curved surfaces (e.g. naso-buccal folds) require interstitial brachytherapy.

Vulvo-vaginal cancers are rare with the average age of diagnosis 70 years and highest incidence in ≥90 years [62,63]. The use of brachytherapy boost in non-operable cases has been on the decline over the past decade despite improved disease specific survival and local control rates with combination treatment [64,65]. A small mixed case series in vaginal cancer showed a trend for improved outcome with combination treatment [66]. Brachytherapy is also a good option in the salvage setting for vaginal recurrence in endometrial cancer with 3-year recurrence free survival at 68% and actuarial rate of late grade 3 toxicity at 8% [67].

Anal squamous cell carcinoma may be treated using an interstitial implant however adoption has been limited with most of the studies use LDR interstitial isotopes requiring general anaesthesia and specialised brachytherapist input. Conflicting results for the benefit of brachytherapy boost in reducing overall treatment time, improving local control has also been reported [68–70]. In locally recurrent disease however, analogous to rectal cancer local surface or interstitial brachytherapy can provide good palliation of pain and bleeding and avoid the need for colostomy in terminal stages of advanced disease.

Addressing barriers to brachytherapy

The barriers to brachytherapy uptake is a global issue and not limited to the elderly population and the onus rests with the radi-

ation oncology community to address the limitations in order to ensure patients are offered the most appropriate radiotherapy modality. A key area that require attention is education and training in brachytherapy.

Developing a brachytherapy curriculum relevant to the global community focusing on the theory beyond current training programs and implementing competency based procedural training would be beneficial for the speciality. Relevant aspects to the elderly population can then be integrated into the global radiotherapy curriculum for elderly cancer patients [71]. The IAEA is currently working on a global curriculum using the CanMEDS framework for brachytherapy professionals however practical training with most countries adopting centralised brachytherapy services still remains a challenge [72]. Competency-based practical training has been recently reported in prostate and cervix brachytherapy with pilot studies consisting of eight trainees. The prostate brachytherapy competency domains were assessed on transperineal rectal spacer placement patients and the cervix on gynecological training pelvic models using tandem and ovoid applicators. Both studies reported an improvement in trainee confidence with the students participating in the cervix study reducing their implant execution time by 10.5% [73,74]. Incorporation of similar training programmes at a national level will address the current issue of low numbers of brachytherapist and not offering brachytherapy as a treatment option to patients. In addition, integrating current coursework materials from international brachytherapy societies, using novel planning-based software with integrated feedback and simulation-based training environments are all tools that should be incorporated in a comprehensive programme. Furthermore, opportunities to undertake dedicated brachytherapy fellowships is currently limited with seven centres in the USA and a collaborative international fellowship in the UK. Other high throughput brachytherapy centres need to establish brachytherapy fellowships for local and international candidates to upskill future radiation oncologists.

Other barriers to improve brachytherapy uptake is to diversify current working models to one that is team-based and not tumour site specific, ensuring the brachytherapist are proficient across tumour streams and to improve advocacy around brachytherapy in particular to address the reimbursement paradox.

Conclusion

The treatment of older patients with cancer continues to present a challenge, as very little high-level evidence exists to guide management. This review highlights the benefits of definitive and palliative brachytherapy in the older population. In aged or frail patients, a comprehensive geriatric assessment is recommended when evaluating individual patient fitness for brachytherapy alongside tumour biology, potential toxicities, physiological age, patient preference, quality of life, and remaining life expectancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] WHO. Ageing and health 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
[2] CRUK. Cancer incidence by age 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero.
[3] Berger NA, Savvides P, Koroukian SM, Kahana EF, Deimling GT, Rose JH, et al. Cancer in the elderly. Trans Am Clin Climatol Assoc 2006;117:147–55. discussion 55–6.
[4] Dodig S, Cepelak I, Pavic I. Hallmarks of senescence and aging. Biochem Med (Zagreb) 2019;29(3):030501.
[5] Kirkhus L, Saltyte Benth J, Rostoft S, Gronberg BH, Hjermstad MJ, Selbaek G, et al. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. Br J Cancer 2017;117(4):470–7.
[6] Fitzpatrick AL, Powe NR, Cooper LS, Ives DG, Robbins JA. Barriers to health care access among the elderly and who perceives them. Am J Public Health 2004;94(10):1788–94.
[7] Kocman D, Regen E, Phelps K, Martin G, Parker S, Gilbert T, et al. Can comprehensive geriatric assessment be delivered without the need for geriatricians? A formative evaluation in two perioperative surgical settings. Age Ageing 2019;48(5):644–9.
[8] Grassi L, Spiegel D, Riba M. Advancing psychosocial care in cancer patients. F1000Res 2017;6:2083.
[9] Kenis C, Decoster L, Van Puyvelde K, De Greve J, Conings G, Milisen K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol 2014;32(1):19–26.
[10] Kunkler IH, Audisio R, Belkacemi Y, Betz M, Gore E, Hoffe S, et al. Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) task force. Ann Oncol 2014;25(11):2134–46.
[11] Popescu T, Karlsson U, Vinh-Hung V, Trigo L, Thariat J, Vuong T, et al. Challenges facing radiation oncologists in the management of older cancer patients: consensus of the international geriatric radiotherapy group. Cancers (Basel) 2019;11(3).
[12] Petereit DG, Frank SJ, Viswanathan AN, Erickson B, Eifel P, Nguyen PL, et al. Brachytherapy: where has it gone? J Clin Oncol 2015;33(9):980–2.
[13] Vu CC, Jawad MS, Krauss DJ. The cost-effectiveness and value proposition of brachytherapy. Semin Radiat Oncol 2020;30(1):87–93.
[14] Halpern JA, Sedrakyan A, Hsu WC, Mao J, Daskivich TJ, Nguyen PL, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. Cancer 2016;122(16):2496–504.
[15] Cancer NCCf. The cost-effectiveness of HDR brachytherapy in combination with external beam radiotherapy in comparison to external beam radiotherapy alone. Prostate Cancer: Diagnosis and Treatment: National Collaborating Centre for Cancer (UK); 2014.
[16] Kim H, Rajagopalan MS, Beriwal S, Huq MS, Smith KJ. Cost-effectiveness analysis of 3D image-guided brachytherapy compared with 2D brachytherapy in the treatment of locally advanced cervical cancer. Brachytherapy 2015;14(1):29–36.
[17] Stahl JM, Damast S, Bledsoe TJ, An Y, Verma V, James BY, et al. Cost-effectiveness of adjuvant intravaginal brachytherapy in high-intermediate risk endometrial carcinoma. Brachytherapy 2018;17(2):399–406.
[18] Ma TM, Harkenrider MM, Yashar CM, Viswanathan AN, Mayadev JS. Understanding the underutilization of cervical brachytherapy for locally advanced cervical cancer. Brachytherapy 2019;18(3):361–9.
[19] Mayadev J, Klapheke A, Yashar C, Hsu IC, Kamrava M, Mundt AJ, et al. Underutilization of brachytherapy and disparities in survival for patients with cervical cancer in California. Gynecol Oncol 2018;150(1):73–8.
[20] Moore KN, Java JJ, Slaughter KN, Rose PG, Lanciano R, DiSilvestro PA, et al. Is age a prognostic biomarker for survival among women with locally advanced cervical cancer treated with chemoradiation? An NRG Oncology/Gynecologic Oncology Group ancillary data analysis. Gynecol Oncol 2016;143(2):294–301.
[21] Benrath J, Kozek-Langenecker S, Hupfl M, Lierz P, Gustorff B. Anaesthesia for brachytherapy–51/2 yr of experience in 1622 procedures. Br J Anaesth 2006;96(2):195–200.
[22] Kobayashi D, Okonogi N, Wakatsuki M, Miyasaka Y, Kiyohara H, Ohno T, et al. Impact of CT-based brachytherapy in elderly patients with cervical cancer. Brachytherapy 2019;18(6):771–9.
[23] Han K, Viswanathan AN. Brachytherapy in gynecologic cancers: why is it underused? Curr Oncol Rep 2016;18(4):26.
[24] Emons G, Tempfer C, Battista MJ, Mustea A, Vordermark D. Statement of the Uterus Committee of the Gynaecological Oncology Working Group (AGO) on the PORTEC-3 study. Geburtshilfe Frauenheilkd 2018;78(10):923–6.
[25] Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92(3):744–51.
[26] Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, 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. Lancet 2010;375(9717):816–23.
[27] Nadaraja S, Jorgensen TL, Matzen LE, Herrstedt J. Impact of age, comorbidity, and FIGO stage on treatment choice and mortality in older danish patients with gynecological cancer: a retrospective register-based cohort study. Drugs Real World Outcomes 2018;5(4):225–35.
[28] van der Steen-Banasik E. Primary brachytherapy as a radical treatment for endometrial carcinoma. J Contemp Brachytherapy 2014;6(1):106–12.
[29] Espenel S, Kissel M, Garcia MA, Schernberg A, Gouy S, Bockel S, et al. Implementation of image-guided brachytherapy as part of non-surgical treatment in inoperable endometrial cancer patients. Gynecol Oncol 2020.

[30] CRUK. Prostate cancer incidence statistics 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence.
[31] Nagaratnam N, Nagaratnam K, Cheuk G. Advanced age geriatric care: a comprehensive guide. Springer; 2018.
[32] Ong WL, Evans SM, Millar JL. Under-utilisation of high-dose-rate brachytherapy boost in men with intermediate-high risk prostate cancer treated with external beam radiotherapy. J Med Imaging Radiat Oncol 2018;62(2):256–61.
[33] Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiotherapy Oncol 2012;103(2):217–22.
[34] Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol 2005;23(6):1192–9.
[35] Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, 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):275–85.
[36] Morton G, McGuffin M, Chung HT, Tseng C-L, Helou J, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiotherapy Oncol 2020;146:90–6.
[37] Hoskin P, Rojas A, Lowe G, Bryant L, Ostler P, Hughes R, et al. High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence. Int J Radiat Oncol Biol Phys 2012;82(4):1376–84.
[38] Dizdarevic E, Frostrup Hansen T, Ploen J, Henrik Jensen L, Lindebjerg J, Rafaelsen S, et al. Long-term patient-reported outcomes after high-dose chemoradiation therapy for nonsurgical management of distal rectal cancer. Int J Radiat Oncol Biol Phys 2020;106(3):556–63.
[39] Rijkmans EC, Cats A, Nout RA, van den Bongard D, Ketelaars M, Buijsen J, et al. Endorectal brachytherapy boost after external beam radiation therapy in elderly or medically inoperable patients with rectal cancer: primary outcomes of the phase 1 HERBERT study. Int J Radiat Oncol Biol Phys 2017;98(4):908–17.
[40] Corner C, Bryant L, Chapman C, Glynne-Jones R, Hoskin PJ. High-dose-rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. Brachytherapy 2010;9(1):66–70.
[41] Appelt AL, Vogelius IR, Ploen J, Rafaelsen SR, Lindebjerg J, Havelund BM, et al. Long-term results of a randomized trial in locally advanced rectal cancer: no benefit from adding a brachytherapy boost. Int J Radiat Oncol Biol Phys 2014;90(1):110–8.
[42] Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. Clin Oncol (R Coll Radiol) 2007;19(9):701–5.
[43] Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85(1):74–80.
[44] Chew DL, Hepburn J, Hoskin P, on behalf of the NICE Colorectal Cancer Guideline Review Committee. Deferral of Surgery for Rectal Cancer: the patients perspective to the recent NICE recommendations. BMJ 2020 [in press]. https://blogs.bmj.com/bmj/2020/08/25/deferral-of-surgery-for-rectal-cancer-the-patients-perspective-on-the-recent-nice-recommendations/
[45] CRUK. Oesophageal cancer statistics 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer.
[46] Dai Y, Li C, Xie Y, Liu X, Zhang J, Zhou J, et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev 2014;10:CD005048.
[47] Rosenblatt E, Jones G, Sur RK, Donde B, Salvajoli JV, Ghosh-Laskar S, et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. Radiother Oncol 2010;97(3):488–94.
[48] Aggarwal A, Harrison M, Glynne-Jones R, Sinha-ray R, Cooper D, Hoskin PJ. Combination external beam radiotherapy and intraluminal brachytherapy for non-radical treatment of oesophageal carcinoma in patients not suitable for surgery or chemoradiation. Clin Oncol (R Coll Radiol) 2015;27(1):56–64.
[49] Shenfine J, McNamee P, Steen N, Bond J, Griffin SM. A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer. Health Technol Assess 2005;9(5:iii):1–121.
[50] CRUK. Lung cancer statistics 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer.
[51] Reveiz L, Rueda JR, Cardona AF. Palliative endobronchial brachytherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2012;12:CD004284.
[52] Pallis AG, Gridelli C, Wedding U, Faivre-Finn C, Veronesi G, Jaklitsch M, et al. Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. Ann Oncol 2014;25(7):1270–83.
[53] Langendijk H, de Jong J, Tjwa M, Muller M, ten Velde G, Aaronson N, et al. External irradiation versus external irradiation plus endobronchial brachytherapy in inoperable non-small cell lung cancer: a prospective randomized study. Radiother Oncol 2001;58(3):257–68.
[54] Tang L, Matsushita H, Jingu K. Controversial issues in radiotherapy after breast-conserving surgery for early breast cancer in older patients: a systematic review. J Radiat Res 2018;59(6):789–93.
[55] Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 2016;387(10015):229–38.
[56] Hannoun-Levi JM, Lam Cham Kee D, Gal J, Schiappa R, Hannoun A, Fouche Y, et al. Accelerated partial breast irradiation in the elderly: 5-Year results of the single fraction elderly breast irradiation (SiFEBI) phase I/II trial. Brachytherapy 2020;19(1):90–6.
[57] Whelan TJ, Julian JA, Berrang TS, Kim DH, Germain I, Nichol AM, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019;394(10215):2165–72.
[58] Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395(10237):1613–26.
[59] CRUK. Non-melanoma skin cancer incidence statistics 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-melanoma-skin-cancer/incidence.
[60] Gauden R, Pracy M, Avery AM, Hodgetts I, Gauden S. HDR brachytherapy for superficial non-melanoma skin cancers. J Med Imaging Radiat Oncol 2013;57(2):212–7.
[61] Tormo A, Celada F, Rodriguez S, Botella R, Ballesta A, Kasper M, et al. Non-melanoma skin cancer treated with HDR Valencia applicator: clinical outcomes. J Contemp Brachytherapy 2014;6(2):167–72.
[62] CRUK. Vaginal cancer statistics 2018. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/vaginal-cancer.
[63] CRUK. Vulval cancer statistics; 2018.
[64] Rao YJ, Hui C, Chundury A, Schwarz JK, DeWees T, Powell MA, et al. Which patients with inoperable vulvar cancer may benefit from brachytherapy in addition to external beam radiation? A surveillance, epidemiology, and end results analysis. Brachytherapy 2017;16(4):831–40.
[65] Mahantshetty U, Naga P, Engineer R, Sastri S, Ghadi Y, Upreti U, et al. Clinical outcome of high-dose-rate interstitial brachytherapy in vulvar cancer: A single institutional experience. Brachytherapy 2017;16(1):153–60.
[66] Laliscia C, Gadducci A, Fabrini MG, Barcellini A, Guerrieri ME, Parietti E, et al. Definitive radiotherapy for primary squamous cell carcinoma of the vagina: are high-dose external beam radiotherapy and high-dose-rate brachytherapy boost the best treatment? Experience of two Italian Institutes. Oncol Res Treat 2017;40(11):697–701.
[67] Vargo JA, Kim H, Houser CJ, Berhane H, Sukumvanich P, Olawaiye AB, et al. Definitive salvage for vaginal recurrence of endometrial cancer: the impact of modern intensity-modulated-radiotherapy with image-based HDR brachytherapy and the interplay of the PORTEC 1 risk stratification. Radiother Oncol 2014;113(1):126–31.
[68] Glynne-Jones R, Sebag-Montefiore D, Adams R, McDonald A, Gollins S, James R, et al. "Mind the gap"–the impact of variations in the duration of the treatment gap and overall treatment time in the first UK Anal Cancer Trial (ACT I). Int J Radiat Oncol Biol Phys 2011;81(5):1488–94.
[69] Hannoun-Levi JM, Ortholan C, Resbeut M, Teissier E, Ronchin P, Cowen D, et al. High-dose split-course radiation therapy for anal cancer: outcome analysis regarding the boost strategy (CORS-03 study). Int J Radiat Oncol Biol Phys 2011;80(3):712–20.
[70] Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer 2010;102(7):1123–8.
[71] Morris LAM, Cree A, O'Donovan A, Simcock R, Thiruthaneeswaran N, Turner S. What every radiation oncologist should know about geriatric oncology: a global expert consensus. Vienna, Austria: ESTRO; 2020.
[72] Abdel-Wahab M, Grover S, Zubizarreta EH, Polo Rubio JA. Addressing the burden of cervical cancer through IAEA global brachytherapy initiatives. Brachytherapy 2020.
[73] Bachand J, Schroeder SR, Desai NB, Folkert MR. Prostate brachytherapy procedural training: incorporation of related procedures in resident training and competency assessment. J Contemp Brachytherapy 2019;11(6):601–6.
[74] Zhao S, Francis L, Todor D, Fields EC. Proficiency-based cervical cancer brachytherapy training. Brachytherapy 2018;17(4):653–9.
[75] Coon D, Beriwal S, Heron DE, Kelley JL, Edwards RP, Sukumvanich P, et al. High-dose-rate Rotte "Y" applicator brachytherapy for definitive treatment of medically inoperable endometrial cancer: 10-year results. Int J Radiat Oncol Biol Phys 2008;71(3):779–83.
[76] Khor R, Duchesne G, Tai KH, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs

external beam radiation therapy alone for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85(3):679–85.
[77] Yamazaki H, Masui K, Suzuki G, Nakamura S, Aibe N, Shimizu D, et al. Radiothrerapy for elderly patients aged >/=75 years with clinically localized prostate cancer-is there a role of brachytherapy? J Clin Med 2018;7(11).
[78] Sur RK, Levin CV, Donde B, Sharma V, Miszczyk L, Nag S. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma–an International Atomic Energy Agency study. Int J Radiat Oncol Biol Phys 2002;53(1):127–33.
[79] Homs MY, Steyerberg EW, Eijkenboom WM, Tilanus HW, Stalpers LJ, Bartelsman JF, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet 2004;364(9444):1497–504.
[80] Bergquist H, Wenger U, Johnsson E, Nyman J, Ejnell H, Hammerlid E, et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. Dis Esophagus 2005;18(3):131–9.
[81] Amdal CD, Jacobsen AB, Sandstad B, Warloe T, Bjordal K. Palliative brachytherapy with or without primary stent placement in patients with oesophageal cancer, a randomised phase III trial. Radiother Oncol 2013;107(3):428–33.
[82] Zhu HD, Guo JH, Mao AW, Lv WF, Ji JS, Wang WH, et al. Conventional stents versus stents loaded with (125)iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. Lancet Oncol 2014;15(6):612–9.
[83] Sharma V, Mahantshetty U, Dinshaw KA, Deshpande R, Sharma S. Palliation of advanced/recurrent esophageal carcinoma with high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2002;52(2):310–5.
[84] Stout R, Barber P, Burt P, Hopwood P, Swindell R, Hodgetts J, et al. Clinical and quality of life outcomes in the first United Kingdom randomized trial of endobronchial brachytherapy (intraluminal radiotherapy) vs. external beam radiotherapy in the palliative treatment of inoperable non-small cell lung cancer. Radiother Oncol 2000;56(3):323–7.
[85] Mallick I, Sharma SC, Behera D, Ghoshal S, Oinam AS. Optimization of dose and fractionation of endobronchial brachytherapy with or without external radiation in the palliative management of non-small cell lung cancer: a prospective randomized study. J Cancer Res Ther 2006;2(3):119–25.
[86] Niemoeller OM, Pollinger B, Niyazi M, Corradini S, Manapov F, Belka C, et al. Mature results of a randomized trial comparing two fractionation schedules of high dose rate endoluminal brachytherapy for the treatment of endobronchial tumors. Radiat Oncol 2013;8:8.