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Palliative radiotherapy: Evolving role and policy challenges

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ABSTRACT

Radiotherapy remains a key modality in the palliation of advanced malignancy managing both local primary tumour effects such as pain and bleeding as well as the sequelae of metastatic disease. Its role continues to evolve in line with advances in radiation technology, which have facilitated dose escalation and reduced toxicity. Injudicious use of such advancements has the potential to magnify the cost of delivering palliative radiotherapy without achieving significant gains in terms of outcomes, and therefore well-designed trials to assess the clinical efficacy are essential. From a policy perspective a key concern remains the heterogeneity in dose fractionation schedules currently utilised internationally which lack a strong evidence base and may be influenced by reimbursement policy that incentivises longer, more complex and less cost-effective schedules.

International consensus is required on study end-points in palliative radiotherapy research to enable comparison between case series and facilitate randomised controlled trial design. Patient reported outcome measures should be developed that capture the value of radiation treatment for different indications both in achieving symptom control but also improving quality of life. The timing and appropriate use of radiation therapy are generally guided by the clinical assessment of the radiation oncologist, once a referral has been made. An analysis of outcomes from national-level epidemiological studies has the potential to guide appropriate utilisation and identify those patients most likely to derive benefit from radiotherapy in different tumour types. Lastly education and training remain at the heart of reducing inequalities in access to radiotherapy for patients who would benefit. This includes both radiation oncologists for whom many training schemes do not prioritise palliative care and the wider multidisciplinary team who are involved in the management of cancer patients at all stages.

Contents

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1. Introduction

Approximately 50% of patients receiving radiotherapy do so with palliative intent [1–3], managing both local primary tumour effects as well as the sequelae of metastatic disease. Increasingly, palliative regimens are also designed to achieve long term control and improve survival, in a population cohort in which disease stage, comorbidities, performance status and patient choice may preclude radical therapy. This has been facilitated by the introduction of radiation techniques such as high dose rate brachytherapy (insertion of radioactive sources directly into the tumour) in addition to new methods of delivering external beam radiotherapy such as intensity modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT).

This review will explore the evolution of palliative radiotherapy in the management of cancer, including the development of new radiotherapy dose schedules aimed at improving long term control and survival, and the integration of new radiation technologies. We will also highlight policy implications of the variation in patterns of palliative radiotherapy delivery and the factors that influence this: practitioner autonomy, radiotherapy access, the paucity of evidence based management guidelines, and the reimbursement policy of different health systems.

2. What guides the delivery of palliative radiotherapy?

The cornerstone of palliative radiotherapy is to achieve symptom control from the effects of the cancer. Symptoms amenable to treatment include: pain, bleeding, neurological dysfunction and luminal obstruction. Patients may receive palliative radiotherapy at diagnosis, relapse or at several points during their disease course. Palliative radiotherapy continues to evolve and it is important to define where the patient lies on their disease pathway: patients with newly diagnosed locally advanced or oligometastatic cancer may have different priorities and clinical aims to those nearing the end of life.

2.1. Locally advanced disease

In patients with symptomatic locally advanced cancer, not treatable radically, the aims are to improve quality of life, delay local progression and possibly improve overall survival. Little work exists looking at optimum radiotherapy schedules and as a result those with the best performance status and longest life-expectancy tend to be offered longer schedules of radiotherapy based on individual clinician experience. In contrast, lower dose regimens of shorter duration are delivered to those with a poor performance status with the aim of rapid amelioration of symptoms.

The use of complex techniques and the actual dose delivered will also be influenced by the site and volume of disease (e.g. proximity to sensitive structures such as the spinal cord, optic chiasm and small bowel). For instance the spinal cord has a dose threshold above which the risk of subsequent myelopathy increases significantly [4]. As such high dose palliative therapy may involve greater utilisation of more complex planning techniques such as IMRT (a technique that allows the high dose region to be tightly conformed to the shape of the target, minimising damage to adjacent normal tissue) [5].

Some evidence based schedules do exist to guide palliative radiotherapy delivery for locally advanced disease with good performance status. In non-small cell lung cancer a meta-analysis revealed no significant difference in symptom control for patients with different radiotherapy schedules ranging from a single fraction to 6 weeks of treatment. However there may be a small survival benefit for good performance status patients receiving higher doses/longer courses of radiotherapy (at least 35 Gy in 10 fractions over 2 weeks), but at the expense of slightly increased toxicity [6].

Glioblastomas of the central nervous system are incurable tumours. However, for good performance status patients a 60 Gy fractionated schedule is recommended with concomitant chemotherapy to improve survival [7]. However, for less fit patients either 30 Gy in 6 fractions over 2 weeks, or best supportive care alone are the treatments of choice [8].

Patients with locally advanced or metastatic cancers of the head and neck are also given high-dose palliative schedules, often over 20 fractions, for local control given potential issues from uncontrolled primary disease such as pain, bleeding, neural compression, dysphagia, and airway compression [9].

2.2. Oligometastatic disease

The concept of the “Oligometastatic State” (OS) was first outlined in 1995 [10]. It was proposed that some tumours progress from a localised to a widely disseminated state, via a stage of limited metastatic disease. The OS can also be “induced” with systemic therapy (i.e. low volume residual macroscopic disease), or arise at relapse. Palliative systemic therapy has traditionally been the treatment of choice for all metastatic solid tumours, although evidence has been accumulating for the use of focal therapy to target more limited disease. The use of focal radiotherapy has followed on from promising results from surgical metastasectomy for lung and liver metastases [11,12].

Compared to surgery, radiotherapy has the advantage of being a minimally invasive out-patient technique, requiring no anaesthetic, and which can target multiple lesions simultaneously, encompassing adjacent subclinical disease. This has the potential to change the natural history of the disease, achieving improved local control, delayed cancer progression, and even cure in selected cases. However whilst randomised trial evidence is awaited, there remains limited clinical evidence to guide patient selection, as evidenced by significant off-label use in the United States (Institute of Medicine 2016). Those likely to derive benefit include patients with low volume metastatic disease (1–3 metastases, small volume), a long disease free interval from treatment of the primary (>6 months), and favourable histology (e.g. breast cancer) [13].

Stereotactic Radiotherapy (SBRT) is rapidly becoming the technology of choice for treating oligometastatic disease. Stereotactic describes the precise irradiation of an image-defined lesion using a high radiation dose delivered in a small number of fractions. When applied outside the brain it is referred to as SABR (Stereotactic Ablative Body Radiotherapy) [14]. This technique requires complex methods of patient immobilisation, target localisation and treatment planning. It is therefore more resource intensive than conventional 2D or even 3D conformal radiotherapy [15,16]. Specialised systems do exist for delivering stereotactic radiotherapy (e.g. Cyberknife®, and Gamma knife®) however it is also possible to deliver such treatments on a modern linear accelerator [17].

For brain metastases a number of treatment options exist including neurosurgical resection, radiotherapy, molecularly tar-

geted agents, best supportive care and combinations. A patient with a favourable prognosis, good performance status, and a lesion less than 4 cm in diameter may be offered surgical resection or stereotactic radiotherapy, with or without whole brain radiotherapy [18]. RTOG 9508 demonstrated that the addition of a stereotactic radiotherapy boost to conventional whole brain radiotherapy improves both overall survival and performance status at 6 months [19]. However for non-stereotactic "whole brain" radiotherapy, no difference has been demonstrated between 5 fraction and 20 fraction regimens in terms of overall survival or local control [20], with around two thirds of patients deriving some neurological benefit.

SABR for lung metastases has reported 2-year local control rates ranging from 70 to 90%, with only minor toxicity (<5% grade 3 toxicity, up to 10% pneumonitis) [21–25]. For liver metastases, SABR data reveals good local control rates in the region of 80% at 2-years, although the majority of patients fail systemically [26].

The key to moving forward is to participate in randomised controlled studies to determine the benefit and cost effectiveness of SABR. The SABR-COMET study is an example, looking at overall survival and quality of life in patients with 1–5 metastatic lesions randomised to standard of care treatment with or without SABR [27].

2.3. Symptom control

Palliative radiotherapy is frequently used for symptom control, often in patients approaching the end of life. In this situation it is important to consider the delay in efficacy when delivering radiotherapy, and the possible short-term flare in symptoms in the context of the patient's anticipated life expectancy. Factors that suggest a lack of benefit from radiotherapy include imminent death, multiple progressive symptoms, anticipated side effects being greater than the symptom being palliated, and poor tolerance of the required journeys for treatment. Clinicians may also advise against re-treatment based on exceeding the safe normal tissue tolerance constraints. Depending on the healthcare model being considered, cost, availability and communication between the palliative care team and the radiotherapy team may also influence referral patterns [28].

Hypofractionated regimens, delivering a low total dose [29], are typically chosen with the aim of achieving rapid amelioration of symptoms at primary or metastatic sites [9,30–32]. They are generally well tolerated, even in patients with poor performance status, and are convenient and cost effective. However, there is marked variation in their use internationally [33]. In the UK the Royal College of Radiologists has published guidelines on optimal dose fractionation schedules according to tumour type and treatment intent [9]. However these recommendations are largely based on single centre retrospective case series given the paucity of randomised control trials evidence [34]. However, some notable exceptions exist.

For lung cancer short course regimens (17 Gy in 2#) have demonstrated equivalent efficacy (symptom control and survival) to longer regimens in patients with poor performance status [35]. In oesophageal cancer dose fractionation regimes considered include 30 Gy in 10 daily fractions, 27 Gy in 6 fractions (treating three times a week) and 20 Gy in 5 daily fractions [36,37]. The addition of High Dose Rate brachytherapy has been found to improve symptom resolution and potentially prolong survival by achieving dose escalation [37]. In bladder cancer, a fractionation schedule of 21 Gy in 3 fractions delivered on alternate weekdays over one week is currently advocated based on a MRC trial, which found no differences in outcomes when compared with 35 Gy in 10 fractions [38].

In cervical cancer one study demonstrated the effectiveness (symptom control) of delivering "quad shots" which involve treating the patient twice a day for two days to a total dose of 14–16 Gy [39,40]. A similar strategy has been advocated for head and neck cancer based on the results of a phase II study [41].

Current international evidence suggests that palliative radiotherapy may be being delivered inappropriately. A number of US studies have shown that up to 50% of patients die before completion of the prescribed radiotherapy schedule [42–44]. Furthermore a significant proportion of patients receiving radiotherapy within the last 30 days of life had multi-fraction treatment. Such practice in the last weeks of life may delay palliative care input, end of life planning and appropriate symptomatic management [28].

It has been suggested that prognostic models could guide both doctors and patients when making decisions about radiotherapy near end-of-life. Doctors tend to be over-optimistic when predicting the life expectancy of patients referred for palliative radiotherapy [45–47] and patients who are overly optimistic in their understanding of their cancer are likely to receive more aggressive treatment [48]. Given that a significant proportion of the total cost of cancer treatment is accrued in the last 30 days of life with little if any impact on outcome [49], it is clear that evidence-based guidelines are essential for optimum patient management. Models have been proposed, but are yet to be adopted into routine practice due to lack of physician engagement and deficits in training. It could be argued that the models are too simplistic and that more profound changes could be achieved by cultural changes in how palliative care is approached, and changing financial incentives to encourage appropriate practices of care, as will be discussed [50].

Whilst evidence based guidelines have focussed on dose and fractionation, the actual decision to refer for radiotherapy or initiate treatment is at the discretion of the individual practitioner. It is therefore based largely on their own personal experience and interpretation of the likely benefit and appropriateness of treatment.

3. Policy issues in palliative radiation oncology

3.1. Variation in access to palliative radiotherapy

Evidence from epidemiological studies has demonstrated that not all patients who may benefit from palliative radiotherapy are receiving it. An analysis of the national radiotherapy dataset for England between 2009 and 2011 demonstrated a trend towards less use of both radical and palliative radiotherapy in the more socioeconomically deprived groups [1].

In the US a study using data from the SEER database (Surveillance, Epidemiology, and End Results-Medicare linked database) identified 51,610 patients with stage IV lung, prostate, breast or colorectal cancer between 2000 and 2007 [51]. The results demonstrated that black men with prostate cancer and lung cancer were 20% and 28% less likely respectively to receive palliative radiotherapy compared to white men.

Another SEER study analysing rates of palliative radiotherapy use in 63,221 patients demonstrated on multivariate analysis that compared to patients aged 66–69, those aged 70–74, 75–79, 80–84, and over 85 had a 7%, 15%, 25%, and 44% decreased rate of receiving palliative radiation, respectively (all $p < 0.0001$) [52]. Other factors associated with lower palliative radiotherapy included increased travel time to a radiotherapy centre, diagnosis at a non-specialist cancer centre and nursing home residence [2,53].

Although epidemiological studies have been valuable in eliciting the factors associated with differential utilisation in palliative radiotherapy this data is limited as it cannot account for differences in disease biology, patient presentation, physician practice and patterns of progression, which may all explain a patient's decision to forgo radiotherapy. Possible reasons may therefore be gleaned from an analysis of the wider literature. For instance we know

that the relative survival of elderly patients with cancer is significantly worse compared to younger persons. The reasons are multifactorial and include, advanced stage at diagnosis, comorbidities, and barriers to accessing cancer services [54–56]. There is strong evidence that elderly cancer patients are more likely to be under-treated (even after adjustment for performance status and other case mix criteria) with many not considered for therapies such as chemotherapy or surgery [57,58]. Training and appropriate utilisation of geriatric screening tools may improve access of elderly patients to palliative radiotherapy [59].

As well as for palliative radiotherapy, ethnic differences have been noted in utilisation of advanced radiation technologies and systemic therapies [60,61]. Potential factors include communication difficulties (language/cultural), and differences in inherent tumour biology [51,62]. Race as with age may also act as a proxy for socioeconomic status, which affect the ability to access and pay for care [63].

Geographical location is also an important factor with several studies demonstrating a correlation between travel time and uptake of cancer treatment (surgery, radiotherapy, chemotherapy) in both the radical and palliative setting [64,65]. This is in part attributable to the increasing centralisation of cancer services, however this has had the resultant effect of increasing travel times for patients and may in fact exacerbate inequities in access and survival outcomes [66–68].

Differential access to palliative radiotherapy may only be overcome through education of practitioners both in the hospital and community setting. There is evidence demonstrating the positive effect of primary care physician education on referral patterns for palliative radiotherapy [69]. Patients also need to be educated specifically about the possible sequelae of metastatic disease and indications for self-referral to a specialist

A lack of radiation oncology engagement with palliative care practice has been identified in a US study. Reasons included limited financial reimbursement, emotional burden of care, insufficient training and knowledge and the reluctance to provide shared care [70]. The onus is on the professional bodies to initiate a change in culture to address these attitudes.

3.2. Reimbursement policy and use of palliative radiotherapy

Goals of palliative radiation therapy should be that the treatment is effective (palliating symptoms and improving quality of life), overall treatment time should be short, convenience for the patient maximised and costs minimised [71]. However a review of fractionation schedules internationally for a variety of palliative indications suggests that we are not adhering to these core principles. A prescient example is the case of uncomplicated bone metastases.

Trial data has confirmed the equivalence of single fraction and multiple fractions of radiotherapy in palliating pain related to uncomplicated bone metastases [72,73]. Furthermore single fraction therapy has been shown to be more cost effective even when accounting for the higher rates of re-irradiation compared to multi-fraction treatment [74]. This prompted the development of consensus guidelines from the American Society for Radiation Oncology (ASTRO) recommending single fraction therapy as the preferred treatment for uncomplicated bone metastases and that no more than 10 fractions should be delivered [30]. Despite this, multi-fraction treatment remains the most popular schedule internationally [33,75,76].

One study in the US looking at fractionation schedules for men with prostate cancer treated for bone metastases found that 3.3% only received single fraction treatment, with 50% receiving greater than 10 fractions [77]. Key differences were noted between academic and both private and community facilities with radiation oncologists working at the latter significantly more likely to deliver multi-fraction treatment [76].

Further analysis demonstrates clear regional differences between practices of care in the US compared to Europe, Canada and Australia [75]. In the Fairchild study respondents trained in parts of Canada or Europe were more than twice as likely to use single fraction regimens, whereas respondents trained in the USA were up to 80% less likely to use a single fraction [33,78]. Unfortunately such variations have a direct impact on the patient in terms of quality of life and convenience of treatment. Equally from a health policy perspective inefficient practices of care are still continuing which affect both the workload faced by radiotherapy departments and contribute to escalating costs of treatment for the health care system [79].

One of the key factors underpinning this variation is the model of reimbursement within individual countries. Lievens has previously [80] reviewed the impact of reimbursement models across Western Europe on fractionation schedules utilised for palliative radiotherapy. A clear differential was seen between countries employing a fee for service model where each component of radiation therapy delivery is reimbursed (simulation, planning, treatment delivery) e.g. Germany and Switzerland, and those employing a global budget or case based system of reimbursement whereby departments are reimbursed per patient or a full treatment course e.g. Spain and The Netherlands.

A fee for service model was associated with an increased likelihood of using multi-fraction schedules for palliation. There is therefore a disincentive for employing efficient practices of care. Of note, the greater use of single fraction schedules in US academic institutions may relate to the fact that many physicians are salaried in these institutions and gain no financial benefit from delivering more fractions. More clearly needs to be done especially given that up to 60% of variation in costs of radiotherapy in the US relate to geography, practice type and individual radiation therapy provider [81].

A further concern is the interface between hospice care and radiation oncology. A survey from the US in the early 2000's found that less than 1% of hospice patients are referred for radiotherapy [82]. Reasons include, the inconvenience of repeated journeys, education deficiencies, life-expectancy and most importantly expense. This has been exacerbated by the predominant utilisation of multi-fraction schedules which can cost upward of $5000 US dollars to deliver, and can dissuade referral due to their inconvenience [33,77]. Furthermore these costs are charged direct to the hospice which has an average daily reimbursement rate of $150 US dollars. A study evaluating the impact of a rapid access radiotherapy clinic offering affordable radiotherapy and minimising waiting times and duration of treatment demonstrated increased referral activity from hospices [83].

In reality country-specific reimbursement models cannot be wholly categorised and usually employ more than one model. For instance in the UK, there has been a move to a reimbursement per attendance or procedure model whereby treatments delivered are reimbursed according to a fixed tariff based on reference costs that are defined nationally [84]. Whilst this may stimulate use of longer fractionation schedules, a driver for continued efficiency is the need to maintain capacity and reduce waiting lists [85,86] to ensure palliative patients are treated within 14 days. In addition patients requiring the treatment of two sites on the same day are still reimbursed as a single attendance.

3.3. Reimbursement policy in the era of technological evolution

The costs of delivering radiation therapy in both the radical and palliative setting continue to increase [87]. Whilst palliative treatment can be delivered quickly, cost-effectively and with low rates of

toxicity using conventional 2D radiotherapy (utilising x-ray localisation and simple beam arrangements), culturally we are moving to use of high dose palliation with more advanced technology.

This has significant financial implications. SBRT for bone metastases costs up to ten times more per treatment [88] when compared with single fraction therapy delivered conventionally and is not cost-effective. However there is an increasing argument to use this modality when life expectancy is estimated to be beyond 12 months, for re-treatment where fields are likely to overlap sensitive structures or in difficult to treat areas such as pelvic recurrence and para-aortic disease [89–91]. Likewise for the management of brain metastases, hippocampal sparing whole brain radiotherapy using IMRT may reduce the late sequelae of treatment, in particular neurocognitive decline [92]. However in most instances the dosimetric advantages of newer technologies are not applicable in the palliative care setting.

Careful patient selection is imperative and we need to avoid a culture of merely using new technology based on their intuitive benefits in the absence of objective data from randomised control trials. Equally reimbursement policies should be realigned to dis-incentivise utilisation of non-evidence based modalities or dose fractionation regimes (e.g. through the introduction of value based user charges [16]).

The provision of evidence based guidelines, use of health technology assessment for evaluating new high cost radiation techniques, and strong reimbursement policy is therefore essential to encourage rational utilisation of new technologies and promote efficient practices of care [93]. "Coverage with evidence development" has been considered to be one mechanism of ensuring access to new technologies which have capacity to improve outcomes whilst collecting data to inform the evidence base about its utility in a real world population [94]. This is the premise for the current assessment of SABR in the NHS [95].

3.4. Education and multidisciplinary management in palliative oncology

Appropriate training and education is also a key aspect of ensuring implementation of evidence based guidelines. A recent survey of Radiation Oncology residents across the US noted key deficiencies in palliative care competencies (e.g. symptom management, care coordination) and most viewed palliative radiation oncology training as inadequate and wished for greater training in these areas [96].

Integrating palliative care into radiation oncology has been attempted through the creation of rapid access palliative radiotherapy clinics (Rapid response Radiotherapy program) which were first developed in Canada [97]. The clinics have reduced waiting times for radiotherapy and ensured multidisciplinary assessment and management of complex patients, focussing on quality of life and symptom control. This model continues to evolve and many examples exist across North America [98].

In the US, although sporadic in their implementation, these integrated palliative care models have helped to improve both radiotherapy access and the proportion of patients treated with single fraction radiotherapy according to evidence based guidelines [99]. They have also reduced the differential practice patterns between academic centres and community centres. Such models provide a forum for knowledge transfer and training of the wider multidisciplinary team as well as helping to support patients and their families.

3.5. Trial endpoints for palliative radiotherapy

Trials within palliative radiation oncology have focussed on the use of differing dose fractionation schedules, combined modality therapies (e.g. chemoradiation), new radiation delivery techniques and defining new indications for treatment (e.g. asymptomatic oligometastases). The list of potential confounding factors is vast given the heterogeneity of disease. From the patient perspective, differences in the extent of functional impairment, impact on quality of life, burden of metastatic disease, performance status, associated comorbidities and extent of previous therapy make evaluation of the efficacy of new radiotherapy techniques and regimes challenging.

As a result the evidence base has largely emanated from single centre retrospective case series which are limited due to poor accounting for case mix variables (age, comorbidity, performance status) and frequently appear to have better outcomes than the benchmark findings from studies in broader unselected, populations. It is therefore imperative that selection bias is overcome by undertaking randomised trials or well-constructed prospective studies that ensure adequate collection of case mix variables and which use validated end points [100]. Whilst there are inherent challenges in designing radiotherapy trials given the rapid software and hardware developments and the variation in practices of care between centres [101], many of these issues do not apply in the palliative setting.

An area of contention is how best to define appropriate trial end-points in palliative radiation oncology. As with systemic therapies, the goal posts are increasingly moving, with end-points such as overall survival (OS) and progression free survival (PFS) increasingly being utilised [102]. This despite numerous qualitative studies involving patients with advanced malignancy demonstrating that improved quality of life is most important goal of therapy [103,104].

Part of the issue is that the term palliative from a radiation oncology research perspective has become very broad and essentially encompasses patients with life expectancies in the region of weeks to those who may survive in excess of 5 years. This confusion is making the selection of end points for trials much harder and the undertaking of systematic reviews more methodologically challenging. An analysis of trials comparing single fraction and multiple fraction treatments for bone metastases [105] found that a major reason for the different conclusions concerning the effectiveness of alternative fractionation schedules was due to the variability in end points used in the studies. As a result consensus guidelines were produced in order to formulate a framework for palliative radiotherapy trials in patients with bone metastases [106]. Similar guidelines for alternative disease sites are imperative to enable meaningful comparison between trials and help define new standards of care.

Progress has been made in the development of quality of life assessment tools that are not only cancer specific but are directed to individuals with advanced disease such as the EORTC QLQ-C30, the QLQ-C15-PAL scales [107]. A bone metastasis specific quality of life tool has also been developed – EORTC QLQ-BM22 [108]. However despite this progress, frequent criticisms of patient reported outcomes measures (PROMS) include both their lack of specificity for radiotherapy related treatment effects and their inadaptability when accounting for rapid changes in technology, thus making comparison difficult with historical studies [109]. Some studies use a number of different questionnaires to get the balance between specificity and generalisability [110] however a number of questions may overlap resulting in differences in PROMS results from the same study [111].

Michael Porter has written eloquently about the need for value based end-points which go beyond traditional methods of assessment including OS, PFS and quality of life [112]. Consideration should therefore be given to assessing alternative outcomes following palliative radiotherapy such as (1) frequency and duration of inpatient admission; (2) frequency of out-of-hours palliative care and GP consultations; (3) return to work; (4) duration of functional

independence. These end-points may help to better evaluate the utility of palliative radiotherapy.

3.6. Evidence framework to guide utilisation of appropriate palliative modality

It is important that evidence based guidelines enable clinicians to select the appropriate palliative strategy (e.g., systemic treatment, radiotherapy, best supportive care) for managing advanced disease. For example a recent meta-analysis reviewed all trials comparing the use of EGFR tyrosine kinase inhibitors with cranial irradiation in patients with brain metastases secondary to EGFR mutant non-small cell lung cancer [113]. As discussed this is challenging especially in terms of defining appropriate trial end-points and selecting patient cohorts for comparison. However such comparisons are necessary given the potential role of radiotherapy in managing patients with oligometastases who previously would have been referred for systemic therapy. If found to be of similar efficacy, radiotherapy may be considered to be advantageous given that apart from fatigue, its systemic effects are minimal and that treatment duration is much shorter [29]. Similar comparisons need to be performed in other indications such as palliation of dysphagia from advanced oesophageal cancer, which may be amenable to treatment with external beam radiotherapy, chemotherapy, endoscopic procedures and HDR Brachytherapy.

3.7. The value of audit in defining practice of care

In the UK, currently all deaths within 30 days of chemotherapy and surgery are audited and subject to retrospective case note review [114]. A similar system has not as yet been employed for radiotherapy but has been recommended as a clinical indicator of avoidance of harm in radiotherapy. There are caveats in using such indicators. For instance it may be impractical given the difficulty in assessing life expectancy. Furthermore the burden of treatment with a single fraction of radiotherapy given the potential palliative benefits is minimal. However auditing 30-day mortality does provide insights into patterns of care which can guide appropriate utilisation of palliative radiotherapy.

A large single centre study in the UK reviewed 30-day mortality rates following palliative radiotherapy for 14,972 palliative episodes, between Jan 2004 and April 2011 and found 30-day mortality rates of approximately 12.3% [115]. Mortality rates were lower in those receiving multi-fraction treatments suggesting that case selection was largely appropriate. Another interesting finding was the higher rates of 30-day mortality for specific tumour types in patients receiving radiotherapy for brain metastases (e.g., melanoma and carcinoma of unknown primary). Further studies are therefore essential to guide appropriate patient selection for palliative radiotherapy and optimise end of life care. It will also help to support the development of trials randomising patients between best supportive care and radiotherapy.

It is also imperative that tumour specific registries and national audits of processes and outcomes of cancer care [116] are set up in order to collect population based data which can be benchmarked against best practice to ensure that inequities in access and variations in practice are highlighted and subsequently addressed [117]. They also help to define new standards of care, especially where limited randomised trial evidence exists to support the use of one technology over another.

4. Conclusions

Radiotherapy is an established and effective treatment modality in the palliation of symptoms associated with advanced cancer. However its role continues to evolve in line with advances in radiation technology. The evidence base remains in its infancy and much more needs to be done to define standards of care in both high and low dose palliation. The latter continues to be the main indication of radiotherapy in advanced disease.

Although clinical acumen is a valuable resource, its individuality has the potential to result in inequalities in care. Multidisciplinary team working, and discussion of patient management in complex cases has the potential to minimise variations in decision making with respect to the utilisation of radiotherapy. In addition, guidance is also required for the wider multidisciplinary team regarding the utility of radiotherapy and benefits of a timely referral.

Given the heterogeneity of international practice, reimbursement policy needs to align with the needs of the patient as many of the current fractionation schedules used for routine indications are both inefficient and are delivered at greater inconvenience to the patient. Likewise given the complexity of managing advanced disease, training and education of all members of both the oncology and palliative care team are necessary in order to ensure radiotherapy is instituted within the appropriate timeframe and delivers outcomes in keeping with patient's wishes. The creation of specialist palliative radiotherapy multidisciplinary teams will facilitate this and improve access to radiotherapy services.

Greater research prioritisation needs to be afforded to developing high-value fractionation schedules for the management of advanced disease that are able to palliate symptoms rapidly, minimising toxicity and maximising convenience to the patients. In the future this may be achieved through multi-modality therapy or use of new radiation techniques but trial evidence ideally needs to inform this. Currently much of the evidence base is derived from single centre retrospective case series where comparison is often not possible due to the use of non-standardised end points. Given the inherent challenges of designing randomised control trials in this cohort, coverage with evidence development, if correctly implemented using standardised end-points and rigorous collection of case-mix variables, offers a potential alternative.

Box 1 Key recommendations to address current policy issues in palliative radiotherapy

- Professional bodies to continue to define standards of care in palliative radiotherapy, specifically dose fractionation schedules.
- Encourage greater use of health technology assessment processes for the evaluation of new radiation techniques in the palliative setting.
- Reconfigure reimbursement policy to incentivise cost-effective palliative radiotherapy practices.
- Use of epidemiological data to enhance our understanding of the outcomes of patients treated with palliative intent to ensure better selection of patients to avoid mortality during treatment.
- Validate and integrate prognostic models into clinical practice to guide utilisation of radiotherapy towards the end of life.
- Consensus guidelines to be developed on trial end-points in different tumour types to facilitate comparison between outcomes from palliative radiotherapy trials.
- Development of specialist palliative care multidisciplinary teams to ensure that suitable patients get rapid access to all appropriate treatment modalities, encourage evidence based practices of care, and improve training and education of all team members including junior staff.

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