Radiotherapy in the control of bleeding from primary and secondary lung tumours

ABSTRACT

This literature review clarifies the role of radiotherapy in the management of low-volume haemoptysis. Embase and Medline were interrogated, and PRISMA guidelines were then used to select relevant articles. Seventy-eight articles were considered relevant and manually reviewed.

The evidence suggests that external beam radiotherapy is more effective than endobronchial brachytherapy at controlling low-volume haemoptysis. There is no evidence to recommend a combination of the two techniques. Different doses and fractionations appear equally effective, with a potential survival advantage of higher dose regimens for fitter patients.

Palliative radiotherapy is effective at controlling low-volume haemoptysis. External beam radiotherapy is the first-line treatment, with endobronchial brachytherapy recommended following external beam radiotherapy failure. Choice of dose and fractionation should take into account the patient's performance status.

The vast majority of patients diagnosed with lung cancer present with locally advanced disease or metastatic disease (Feinstein and Wells, 1990), the symptoms of which can have a significant impact on quality of life. Haemoptysis is the expectoration of blood into the lower airways; in lung cancer it is commonly caused by bleeding from the tumour invading into the adjacent airway. It is a common presenting complaint of primary lung cancer and can remain a significant burden for the patient throughout the course of his/her disease. The estimated prevalence in patients with primary lung cancer is 25–50% (Chute et al, 1985; Hirshberg et al, 1997). Endobronchial pulmonary metastases that cause symptomatic haemoptysis are relatively rare. The most common primaries responsible are breast, colorectal and renal carcinoma (Dobbertin, 1999; Lee et al, 2013).

The management of haemoptysis is dependent on the volume of blood expectorated. The anatomical dead space in the lungs is approximately 200 ml (just less than half a pint). Therefore volumes approaching this can quickly compromise gas exchange and require immediate resuscitation, intervention (bronchoscopy, arteriography) or rapid palliation. Medical therapies such as tranexamic acid and reversal of anticoagulation for management of haemoptysis are also important (Prutsky et al, 2016). Low volume haemoptysis can effectively be managed by palliative radiotherapy on an outpatient basis. This review provides a general overview of the management of small volume haemoptysis in the context of lung cancer and discusses what is currently available with regard to the use of external beam radiotherapy and (in some circumstances) endobronchial brachytherapy.

Literature review

Two large systematic reviews have been performed to identify the optimum radiotherapy treatment schedule and dose for palliative thoracic radiotherapy in lung cancer – the first by Fairchild et al (2008) and then a Cochrane review by Stevens et al (2015). The difference between the two is that Fairchild et al (2008) identified a small survival benefit in patients who received a higher dose of radiotherapy whereas the Cochrane review did not find a dose–response effect.

For this article, the search strategy was addressed through the precise identification of Participants, Interventions, Comparisons and Outcomes (PICOS criteria) in Medline and Embase platforms.

In Medline the search strategy ((((lung* OR pulmonary).ti,ab AND (cancer* OR tumor* OR tumour* OR neoplasm* OR carcinoma*).ti,ab) OR "LUNG NEOPLASMS"/) AND ((brachytherapy OR radiotherapy OR "radiation therapy" OR imrt OR igrt).ti,ab OR exp RADIOTHERAPY/)) AND ((haemoptysis OR hemoptysis).ti,ab OR HEMOPTYSIS/) was used, which gave 323 results.

The same strategy was repeated in Embase, being more specific and restricting to the palliative setting in order to get a reasonable numbers of article for manual review: (((((lung* OR pulmonary).ti,ab AND (cancer* OR tumor* OR tumour* OR neoplasm* OR carcinoma*).ti,ab) OR "LUNG TUMOR"/) AND ((brachytherapy OR radiotherapy OR "radiation therapy" OR imrt OR igrt).ti,ab OR exp RADIOTHERAPY/)) AND ((haemoptysis OR hemoptysis).ti,ab OR HEMOPTYSIS/)) AND ((palliative).ti,ab OR exp "PALLIATIVE THERAPY"/). This strategy produced 297 records. The PRISMA

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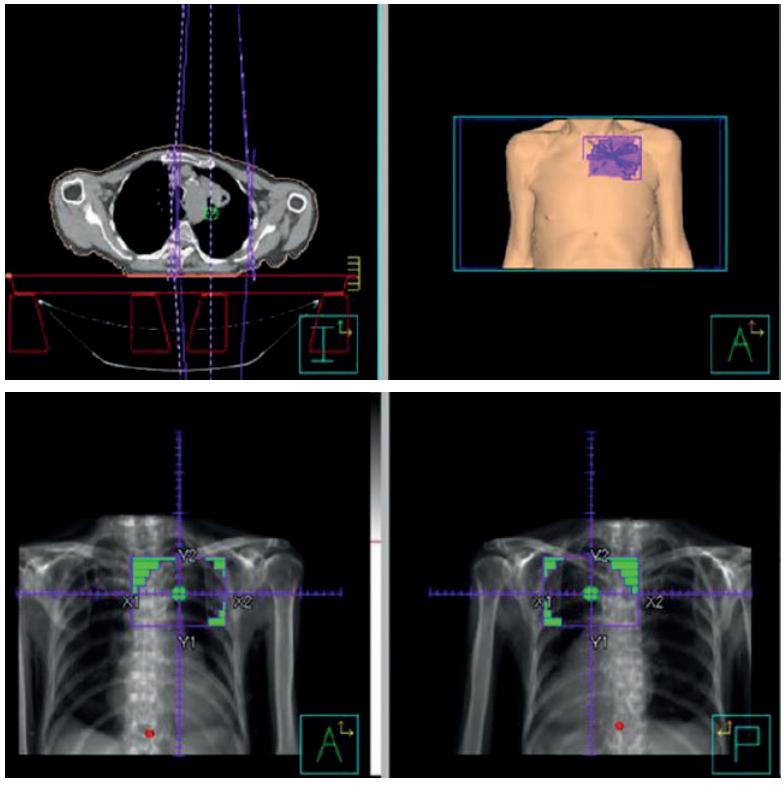
(Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were then used to select relevant articles. Records were excluded if they were not inherent to lung (either primary or secondary) malignancies, if radiotherapy was used with a curative aim at radical doses rather than in the palliative setting, if surgical procedures or systemic treatments were used to obtain haemostasis, or if they were not in English. Duplicates were also excluded.

Seventy-eight articles were considered relevant and were manually reviewed. The literature search did not reveal any further relevant systematic reviews or randomized controlled trials discussing the role of external beam radiotherapy for haemoptysis published after the Cochrane review.

Figure 1. A conventional linear accelerator used for external beam radiotherapy.

Figure 2. The same case showing: **(a)** the beam setup, **(b)** two (anterior and posterior) beams are assigned to this prescription; surface rendered view of the radiotherapy field. Inferiorly, **(c)** anterior and **(d)** posterior beam's eye view digitally reconstructed radiograph.



External beam radiotherapy

Palliative radiotherapy to the lung is used to manage symptoms of lung cancer. The mainstay of this treatment is external beam radiotherapy. This uses megavoltage photons produced by a linear accelerator (*Figure 1*) to treat the macroscopic gross tumour volume with a margin to cover for non-visible disease. It is commonly delivered using a parallel opposed field (one field posteriorly and one anteriorly, *Figure 2*). Each treatment can be delivered in a matter of minutes to a patient lying supine.

The overall dose of radiotherapy is split into individual treatments. This method is called fractionation, which refers to the amount of radiotherapy (expressed in Gray, Gy) delivered to the tissue per treatment. There are multiple proposed fractionation regimens which will be discussed. The benefit of fractionation is that it allows the normal (non-cancerous) tissue to repair, enabling a higher dose to be delivered to the tumour without compromising other structures and tissues in the thorax.

It is important to note that, with palliative radiotherapy, even a patient with a poor performance status can gain a significant amount of relief from haemoptysis by using one (10 Gy) or two fractions (17 Gy) of radiotherapy. For higher dose regimens three-dimensional conformal radiotherapy or intensity-modulated radiotherapy is often used as this can spare normal tissue and reduce toxicities such as oesophagitis. This would require patients to be treated with arms elevated or, for apical tumours, potentially using immobilization with a shell.

Endobronchial brachytherapy

The second type of radiotherapy treatment is high dose endobronchial brachytherapy. The Greek word 'brachy' or brachios means close, so brachytherapy is the placement of a radioactive source (more commonly iridium-192) in close proximity to the tumour, using bronchoscopy to position the source. The catheters used for brachytherapy are approximately 10 cm long, but the active source is only a few millimetres long. The dose delivered is expressed in Gy.

Brachytherapy dose is usually prescribed 1 cm laterally from the axes of the catheters and the reference isodose (maximum dose area) is supposed to cover the visible endobronchial tumour plus a reasonable margin (2 cm) of bronchial segment proximal and distal to the tumour (Anacak et al, 2001).

The advantages of brachytherapy include delivery of a greater dose to the tumour and lower toxicity to the surrounding tissues. This can be delivered in one to three fractions. There is evidence that following this patients have good and durable responses to the haemoptysis but with the added complications of requiring bronchoscopy (Ozkok et al 2008; Zaric et al 2010). A Cochrane review (Reveiz et al, 2012) compared endobronchial brachytherapy *vs* external beam radiation therapy *vs* a combination of endobronchial

brachytherapy and external beam radiation therapy. External beam radiotherapy was more effective for symptom control than endobronchial brachytherapy and there was no evidence to recommend a combination of external beam radiotherapy and endobronchial brachytherapy. There was no survival benefit between the two techniques. Reviews of the data performed by the American Brachytherapy Society (Stewart et al, 2016) and ASTRO (American Society for Radiation Oncology) recommendations (Rodrigues et al, 2011) agreed with this assessment. Therefore external beam radiotherapy is the initial treatment for symptom relief, with the potential for endobronchial brachytherapy for relapse, especially if obstruction or haemoptysis are problematic (Stewart et al, 2016).

Efficacy

Although the trials included in the Fairchild et al (2008) and the Cochrane reviews (Stevens et al, 2015) were not specifically looking at the resolution of haemoptysis, they did report the effect of different treatment regimens on the main lung symptoms. Of the trials in the Fairchild et al (2008) review five reported the number of patients who had a complete resolution of haemoptysis following radiotherapy (Anonymous, 1991, 1992; Rees et al, 1997; Nestle et al, 2000; Erridge et al, 2005).

Rees et al (1997) performed a prospective randomized trial comparing 17 Gy in two fractions *vs* 22.5 Gy in five fractions and found no difference between them; 97% of patients showed an improvement in haemoptysis, which was maintained in over 50% of patients for 8 weeks or more.

Nestle et al (2000) compared 60 Gy in fractions of 2 Gy per day for 5 days a week with 32 Gy delivered in two daily fractions of 2 Gy. They observed no difference between the two treatment groups.

Erridge et al (2005) compared 10 Gy in one fraction *vs* 30 Gy in 10 fractions in 149 patients. The difference between the two groups was not statistically significant but supported the efficacy of external beam radiotherapy in managing haemoptysis.

A Medical Research Council trial (Anonymous, 1991) compared 17 Gy given in two fractions of 8.5 Gy 1 week apart or a conventional multifractionated regimen of either 30 Gy in ten fractions or 27 Gy in six fractions. The overall complete response rate was 81% (two fraction arm) and 86% (conventional fractionation arm). The median duration of response was 50% or more of survival.

Another Medical Research Council (Anonymous, 1992) multicentre randomized controlled trial compared 17 Gy given in two fractions of 8.5 Gy 1 week apart (F2 regimen, 117 patients), or a single fraction of 10 Gy (Fl regimen, 118 patients). Again there were minimal differences between the group but this demonstrated a good response in general for haemoptysis.

The remaining four trials (Simpson et al, 1985; MacBeth et al, 1996; Sundstrøm et al, 2004; Senkus-Konefka et al, 2005) also discussed the effect of radiotherapy on lung cancer symptoms as their primary endpoints. The response of haemoptysis was documented although the completeness of response was not documented.

Simpson et al (1985) randomized 409 patients to a 40 Gy split course over 4 weeks, 30 Gy over 2 weeks or a 40 Gy continuous courses over 4 weeks. Palliation of haemoptysis was achieved in 77%, 74% and 73% across these treatment arms.

A further Medical Research Council (MacBeth et al, 1996) randomized controlled trial involved 509 patients allocated to either 17 Gy in two fractions (F2) 1 week apart or 39 Gy in 13 fractions (F13) 5 days per week. They estimated the cumulative percentages of patients with improvement of haemoptysis at 3 months as 95% (two fraction regimen) and 89% (13 fraction regimen) in the two arms.

Sundstrøm et al (2004) had a three-arm randomized trial which assessed 395 patients. The three arms were 17 Gy in two fractions, 42 Gy in 15 fractions and 50 Gy per 25 fractions. There was no statistical difference between the regimens but again they showed the efficacy of radiotherapy.

Senkus-Konefka et al (2005) performed a randomized controlled trial of 100 patients. The two treatment arms were 20 Gy in five fractions (arm A) or 16 Gy in two fractions 1 week apart (arm B). Although there were low numbers of patients they demonstrated an improvement in 80% (A) and 100% (B) of patients, although the difference between the two arms was not statistically significant.

Overall the meta-analysis from Fairchild et al (2008) estimated that across the trials 80.2% of patients in the lower dose arms and 81.2% in the higher dose arms had some improvement in haemoptysis.

The Cochrane review (Stevens et al, 2015) reached the same conclusions, identifying that all 13 trials showed some form of improvement in all symptoms including haemoptysis.

Optimum fractionation

One of the biggest debates in palliative radiotherapy to the lung is the fractionation schedule. In terms of management of bleeding there is no clear evidence that any dose or fractionation is superior. The options for fractionation vary from one fraction schedules for frail patients to 2–3 weeks' treatment for fitter ones.

Early randomized controlled trials attempted to identify the optimum dose and fractionation schedule. As previously mentioned the UK Medical Research Council performed three randomized controlled trials (Anonymous, 1991, 1992; MacBeth et al, 1996). None of these trials identified any significant difference in efficacy or survival benefit between the different fractionations.

The systematic review by Fairchild et al (2008) concluded that increasing the dose and fractionation might provide a small survival advantage, but this was in extremely fit patients with limited disease, at a cost of increased toxicity and increased hospital visits. The Cochrane review (Stevens et al, 2015) felt there was not sufficient evidence to

recommend higher dose regimens. The current Scottish Intercollegiate Guidelines Network (2014) guidance recommends a higher dose regimen of 39 Gy in 13 fractions for patients who have good performance status, and a lower dose regimen of one or two fractions for those with a poor performance status.

The ASTRO consensus (Rodrigues et al, 2011) agreed that there was an improvement in survival and palliation of symptoms in patients with a favourable performance status. For patients with a poor performance status they recommend shorter regimens such as 20 Gy in five fractions, 17 Gy in two weekly fractions, or 10 Gy in one fraction.

Side effects

Toxicity is reported using the acute radiation morbidity scoring criteria. Grade 1 reactions include mild symptoms that are tolerated by the patient. Grade 2 side effects are those that require intervention as an outpatient. Grade 3 are side effects that require inpatient management and grade 4 are those that are life threatening. Although external beam radiotherapy is generally well tolerated it does carry a risk of both acute and late toxicities. As with all forms of radiotherapy, general malaise and fatigue are frequently reported.

More specifically the oesophagus, with its close proximity to the treated area, is one of the most important organs at risk for radiotherapy to the lung. Oesophagitis can result in dysphagia and subsequently poor nutrition and hydration and increasing need for analgesia. It is unfortunately common (Anonymous, 1991, 1992; MacBeth et al, 1996).

The Medical Research Council trials found that dysphagia lasted longer (MacBeth et al, 1996) and occurred more frequently (Anonymous, 1992) in the high dose arms.

Fairchild et al (2008) found that the incidence of dysphagia was significantly higher in the higher dose treatment arm (20.5% *vs* 14.9%) whereas Stevens et al (2015) could not make a clear recommendation that higher dose regimens had a higher incidence of oesophagitis. Regardless of its relationship to dose oesophagitis is one of the most important side effects of palliative radiotherapy and patients need to be consented and observed throughout treatment for this.

Radiation pneumonitis is a rare and normally mild (although it can be life threatening) consequence of thoracic radiotherapy. It is felt to be caused by a combination of damage to the DNA of the lung tissue and the subsequent acute inflammatory response. Radiation pneumonitis is characterized by fever, breathlessness, cough, hypoxia and infiltrates seen on a chest X-ray. With a clinical picture often indistinguishable from pneumonic infiltration it is an important differential to consider in any patient presenting with respiratory symptoms post-thoracic radiotherapy. Radiation pneumonitis tends to be transient and settles post treatment but supportive measures such as steroids, diuretics and respiratory support can be required. It tends to occur between 2 weeks and 6 months after completion of therapy.

Stevens et al (2015) confirmed that this is a rare event with an estimated frequency of 1.6–6% across the trials reported; there is some evidence that the incidence is less in fractionated regimens. Fairchild et al (2008) estimated a frequency of 3.6% in high dose treatment arms and 1.8% in lower dose arms. Patient information and education of clinical staff is important to identify the small number of patients who present with radiation pneumonitis.

Radiation myelopathy (characterized by neurological deficit secondary to damage and inflammation of the spinal cord) is thankfully rare, reported only six times in the literature. This may be because the timescale to develop myelitis is around 18 months therefore may not be a major consideration for patients with limited prognosis.

Metastases and small cell lung cancer

As mentioned the systematic review performed by Fairchild et al (2008) included both patients with non-small cell lung cancer (95%) and small cell lung cancer (5%). Patients with small cell lung cancer were only included in two of the trials, so there is limited literature to inform advice for this patient group.

There is very little evidence for the management of symptomatic metastatic disease. For oligometastatic disease there is literature to suggest that stereotactic radiotherapy to high risk central pulmonary metastasis is potentially a safe and effective treatment (Lischalk et al, 2016). For symptomatic endobronchial lesions (metastasis near the bronchial tree) a small prospective cohort of 35 patients by Donovan et al (2017) used intraluminal brachytherapy. Patients were treated with 700 cGy of brachytherapy over three fractions. Roughly half (17/35) had been treated with external beam radiotherapy previously. They showed a 75% improvement in haemoptysis, and median symptom-free and overall survival was 67 and 117 days.

Ultimately the management of these patients will likely be undertaken on a case-by-case basis.

Conclusions

It is important to note that radiotherapy to control bleeding from the upper airways is only appropriate if this is a small volume because of the time required for planning and delivering treatment, and the fact that a response is not immediate. External beam radiotherapy is undoubtedly an effective treatment for palliation of symptoms from locally advanced lung cancer and should be considered in all patients with small volume bleeding secondary to lung cancer. Two systematic reviews performed in the context of primary lung cancer by independent groups provide robust data to support this.

External beam therapy is the preferred treatment modality, with external beam brachytherapy being reserved for those who experience recurrence or symptoms related to endobronchial obstruction following external beam radiotherapy. The majority of patients tolerate the treatment well with the most commonly reported side effect being transient dysphagia. Regarding fractionation

the evidence that higher dose palliative radiotherapy prolongs survival is not strong, and the cost of this maybe increased toxicity. It is reasonable to give higher doses in patients with good performance status but in those that are frail outcomes appear to be no different with few fractions and an overall lower dose. Patients with small cell lung cancer or endobronchial metastasis are routinely treated in a similar manner using palliative external beam radiotherapy, but there is limited evidence to demonstrate the efficacy of this approach. **BJHM**

Conflict of interest: none.

KEY POINTS

- All patients with small volume symptomatic bleeding from lung tumours should be considered for radiotherapy and discussed with an oncologist.
- There is good evidence that low dose regimens can be delivered quickly and effectively, even to patients who have had a deterioration in their performance status.
- Differing doses and fractionations appear equally effective, although for fitter patients who will tolerate them there is potentially a survival advantage with higher dose regimens.
- Brachytherapy is only recommended after external beam radiotherapy failure.
- There is limited evidence regarding the use of radiotherapy in patients with small cell lung cancer or metastatic disease from an extrapulmonary source.

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