Interventional oncology in multidisciplinary cancer treatment in the 21st century

Andreas Adam and Lizbeth M. Kenny

Abstract | Interventional oncology is an evolving branch of interventional radiology, which relies on rapidly evolving, highly sophisticated treatment tools and precise imaging guidance to target and destroy malignant tumours. The development of this field has important potential benefits for patients and the health-care system, but as a new discipline, interventional oncology has not yet fully established its place in the wider field of oncology; its application does not have a comprehensive evidence base, or a clinical or quality-assurance framework within which to operate. In this regard, radiation oncology, a cornerstone of modern cancer care, has a lot of important information to offer to interventional oncologists. A strong collaboration between radiation oncology and interventional oncology, both of which aim to cure or control tumours or to relieve symptoms with as little collateral damage to normal tissue as possible, will have substantial advantages for both disciplines. A close relationship with radiation oncology will help facilitate the development of a robust quality-assurance framework and accumulation of evidence to support the integration of interventional oncology into multidisciplinary care. Furthermore, collaboration between interventional oncology and radiation oncology fields will have great benefits to practitioners, people affected by cancer, and to the wider field of oncology.

Adam, A. & Kenny, L. M. *Nat. Rev. Clin. Oncol.* advance online publication 2 December 2014; doi:10.1038/nrclinonc.2014.211

Introduction

Interventional oncology is a term used for a group of interventional radiological procedures used in the cure and palliative treatment of cancer. It is a newly developing discipline and its development varies substantially even within developed countries with advanced technologies. The role of interventional oncology can be defined, at least in part, in relation to the two disciplines that are most-closely related to it: its parent specialty of diagnostic radiology and its sister discipline of radiation oncology.

Both radiation oncology and interventional oncology rely on sophisticated technological equipment to achieve nonsurgical local control, cure or palliative care of cancer. Apart from a small number of ablative techniques such as radiosurgery, stereotactic ablative radiation therapy (SABR) or stereotactic body radiation therapy (SBRT), in which a limited number of high dose fractions are delivered, radiation therapy overall aims to protect and preserve the structure and function of normal tissue. By contrast, interventional oncology, when used with a curative purpose, usually relies on ablative methods. Both disciplines require sophisticated imaging for planning and guidance and work in an environment of rapidly evolving technology.

Diagnostic radiology and radiation oncology have common origins. For more than half a century, both fields were intimately linked in terms of training and clinical practice. Indeed, in some countries, these disciplines remain closely linked, whereby future radiologists and radiation oncologists are being taught together at the beginning of their training or both disciplines are taught within one professional college or society. However, during the 1950s, the two disciplines started to separate and, in many countries, took entirely different paths. Diagnostic radiology increasingly distanced itself from patients, with radiology technicians obtaining the images and radiologists focusing on their interpretation, whereas radiation oncology gradually established itself as a mainstream clinical discipline and is firmly entrenched as a cornerstone of multidisciplinary cancer care.

Developments in imaging, as well as changes in the clinical role of interventional radiologists, are leading to a degree of overlap and convergence between interventional oncology and radiation oncology. We believe that a close collaboration between the two disciplines will have great benefits for patients and the health-care system as a whole. Collaboration is the key to ensure that patients can access all appropriate treatment options and that the spectrum of local treatment techniques continues to expand.

In this Review, we examine the current role of interventional oncology and its relationships with other disciplines involved in cancer care. We focus particularly on radiation oncology, because we believe that a close relationship of interventional oncology to this discipline might have a decisive influence on future interventional oncology techniques. We also make suggestions on how collaboration between radiation oncology and interventional oncology can benefit patients.

Department of Radiology, Guy's and St Thomas' Hospitals NHS Foundation Trust, 1st Floor Lambeth Wing, Westminster Bridge Road, London SE1 7EH, UK (**A.A.**). Cancer Care Services, Royal Brisbane and Women's Hospital, Herston, Brisbane, QLD 4029, Australia (**L.M.K.**).

Correspondence to: A.A.
andy.adam@kcl.ac.uk

Competing interests
The authors declare no competing interests.

Key points

- Interventional oncology is a new discipline, which uses minimally invasive, image-guided techniques to treat patients with cancer
- Percutaneous thermal ablation and cryotherapy are the main potentially curative methods of treatment used by interventional radiologists when treating patients with cancer
- Both interventional oncology and radiation oncology can achieve local cure of malignant tumours
- Collaboration between radiation oncologists and interventional oncologists would have important benefits for patients with cancer and for both of these disciplines

Radiation oncology

Until recently, radiation therapy, either alone or in combination with chemotherapy, was considered as a second-line treatment for many conditions and was used mainly when surgery was not possible.[1–4] However, radiation therapy has evolved and is now a highly sophisticated, cost-effective, primary method of treatment for many people with cancer. It cures many patients, and can be very effective in the relief of symptoms for those in whom curative treatment is not feasible.

All forms of radiation treatment that are available today (external beam treatment with photons or particles, brachytherapy and radionuclides), have been made possible by an extraordinary collaborative effort between committed researchers in the fields of biology, physics, chemistry, and clinical medicine over 12 decades.[5] Since the mid-1950s when linear accelerators came into mainstream clinical use, radiotherapy technology has advanced greatly. The aim of radiation therapy is, and has always been and will be, to maximally treat cancer tissue and spare normal tissue. All evolving techniques, both technical and radiobiological, aimed at improving dose delivery, are driven by these principles.[5–7] Technological advances such as the development of intensity modulated radiation therapy (IMRT) enable the shaping of beams with very steep dose gradients, which can deliver high doses to cancer tissue while sparing the adjacent healthy tissues and organs. The effective use of such technology requires a deep understanding of anatomical and molecular imaging, tumour and normal tissue biology, and treatment-related risk factors. A greater understanding of the biology of cancer and radiobiology has enabled more-effective exploitation of the benefits of combined modality treatment. The evidence underpinning the use of radiotherapy is based on a large number of scientific studies, carried out over many decades. Delaney and colleagues analysed and assessed these studies methodically and determined that approximately 50% of patients with cancer would benefit from radiation treatment.[8]

In most developed countries, radiation oncologists usually work within multidisciplinary teams. Radiation treatment can be used as a sole curative modality in some circumstances, but is more frequently combined with surgery and systemic therapy to maximize both local and systemic disease control. Over 80% of the indications for radiotherapy are aimed at improving the likelihood of cure.[9] Radiation treatment will often enable less-radical surgery to be used (for example, in the conservative treatment of limb sarcomas and in breast cancer), or might replace surgery altogether (as in the case of many patients with oropharyngeal cancer). The integration, sequencing and linking of combined modality treatments and collaboration between radiation oncologists and other members of multidisciplinary teams are vital to ensure access to high-quality cancer treatment. These principles are directly applicable to interventional oncology.

Interventional radiology

Interventional radiology is a unique field; it is an acute, front-line clinical discipline that emerged from within a diagnostic specialty. The increasingly sophisticated and intricate techniques that were developed in diagnostic angiography provided the opportunity to adapt them for the treatment of patients. The performance of the first angioplasty by Charles Dotter in 1964 heralded the era of minimally invasive therapy.[10] Today, interventional radiologists treat conditions in almost every organ in the body. Their techniques cause minimal trauma to normal tissues, enabling rapid recovery and early return to work. Moreover, interventional radiology techniques are less expensive than equivalent surgical methods, as they involve a shorter stay in hospital and are usually accompanied by fewer complications than surgery.[11,12]

The treatment of vascular conditions has always been an important part of interventional radiology. Vascular interventions are now mainstream treatment for aortic aneurysms, arterial and venous stenosis or obstruction, and traumatic or gastrointestinal haemorrhage.[13–22] In many countries, vascular surgeons and cardiologists have learned to use interventional radiological techniques to treat patients with vascular disease, reducing the involvement of interventional radiologists in this field. However, new techniques have emerged, which have increased the role of interventional radiology in the treatment of malignant disease, thus providing new opportunities for interventional radiologists, and expanding treatment options for people affected by cancer.

Interventional radiology in oncology

Palliative application

Interventional radiology procedures have been used in both the palliative and curative treatment of cancer. Until recently, all interventional radiological procedures in the field of oncology were palliative rather than curative. Palliative procedures, such as the drainage of malignant ascites and pleural collections, can improve the quality of life of patients with cancer. Percutaneous nephrostomy can maintain renal function in patients with obstruction of the urinary tract;[23] however, the presence of drainage bags severely reduces the quality of life of the patient. Ureteric stenting achieves similar benefits without the need to use unsightly bags or external catheters.[24–26] Percutaneous biliary drainage has also made a major contribution to palliative care, as it enables the relief of jaundice and the elimination of the unpleasant physical and psychological consequences of the retention of bile.[27] Internal stents have increased the attractiveness of biliary drainage, as they enable bile to flow into the duodenum,

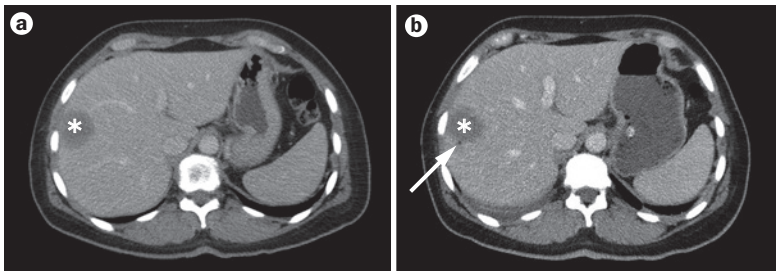

Figure 1 | Thermal ablation of hepatic metastasis in a female patient with breast cancer. **a** | This preoperative CT image shows an area of low attenuation (asterisk) in the right lobe of the liver, which represents a metastasis. This was treated with a radiofrequency electrode for 12 minutes. **b** | Following radiofrequency ablation, the tumour has been coagulated. As observed in the postoperative CT image, the region is now of lower attenuation and contains a small bubble of gas at its inferior margin (arrow). The area of low attenuation appears slightly larger than before treatment, as the coagulated area exceeds the size of the tumour.

thus helping to improve the patient's nutritional status and to avoid the complications of external biliary drainage.[28,29] Self-expanding metallic biliary endoprostheses have revolutionised this field, as they have enabled effective internal drainage without the risks and discomfort associated with the insertion of fixed-size conventional biliary stents.[30–33] Most biliary endoprostheses are now inserted endoscopically, but percutaneous insertion remains needed when endoscopic access is difficult or impossible.[34,35] Metallic stents have also made a major contribution to the palliative care of patients with oesophageal, duodenal, colorectal and bronchial malignant obstruction.[36–50] Rigid plastic oesophageal tubes were not particularly effective in achieving adequate nutrition because of their relatively small lumen, which permitted only a liquid or semi-liquid diet, whereas metallic self-expanding oesophageal stents make it possible for patients to eat almost normally. Tracheobronchial stents can relieve distressing stridor and frequent episodes of pneumonia in patients with malignant bronchial obstruction.

Palliative interventional radiological procedures are often carried out as part of a 'technical' service offered to patients under the care of another physician. In this setting, it is usually inappropriate for the interventional radiologist to assume primary clinical responsibility for the patient being treated. Nevertheless, the performance of such procedures in an environment in which the interventional radiologist is not sufficiently well integrated into the clinical team caring for the patient has important disadvantages. The optimum use of palliative interventional radiological procedures, or the decision of whether or not to use them, requires an informed discussion between the referring physician, the interventional radiologist and the patient. When such procedures are performed simply in response to written requests, as for diagnostic investigations, important information that can influence the decision of which technique to use or whether or not to proceed with the procedure might be overlooked. For example, a patient with malignant obstructive jaundice who could be a candidate for surgery, might be best treated with a plastic endoprosthesis, which can be easily removed before, or at the time of, surgery, whereas a similar patient who cannot be treated surgically might be best palliated with a self-expanding metallic endoprosthesis. The relevant information does not always appear on request forms; therefore, personal communication between the specialists involved in the care of the patient, ideally at a meeting of a multidisciplinary team, ensures optimum care and avoidance of potentially irreversible errors.

Curative application

In the past few decades, potentially curative interventional radiological methods of treatment, such as ablation of tumours with lasers, radiofrequency energy (Figure 1), microwaves, cryotherapy and irreversible electroporation, have emerged,[51–57] and have been combined with palliative techniques to create the discipline of interventional oncology. Initially, such procedures were seen as 'optional extras', and were used in patients with cancer in whom other methods of therapy had failed or could not be used. However, as the number of patients treated by interventional radiological methods increased, it became obvious that, for at least some conditions, these techniques provide an attractive alternative to surgery. For example, small renal tumours can be ablated using percutaneous techniques with minimal morbidity, a short stay in hospital and preservation of renal function.[58–62] In the liver, thermal ablation methods have similar outcomes to surgery in the treatment of hepatocellular carcinoma and are proving to be increasingly important in the management of liver metastases that are not amenable to surgical resection.[63] In addition, percutaneous or intraoperative ablation of hepatic metastases combined with surgical resection have been shown to be effective in patients in whom either treatment modality alone is considered inappropriate.[64–66] Moreover, radioembolization and chemoembolization are useful methods of stabilization of disease in patients in whom surgery or ablation are not appropriate.[67–70] Percutaneous ablation is also increasingly used in the treatment of primary and metastatic malignant tumours in the lung. The high local recurrence rate associated with radiofrequency ablation has led to increased use of microwave and cryotherapy techniques, with promising results.[71–76]

The number of patients who could benefit from potentially curative interventional radiological techniques is much larger than those actually referred to interventional oncologists. An important reason for the limited access to this discipline is the lack of an adequate number of interventional radiologists. There is a general lack of knowledge of what interventional oncologists have to offer. Interventional radiological treatments feature little in international treatment guidelines owing to both a lack of evidence and a lack of representation on guideline panels. An additional notable reason for the underuse of interventional radiology is the difficulty to sustain a practice in interventional oncology without assuming clinical responsibility for the patient to the same extent as specialists in other treating disciplines. Many interventional radiologists do not have the time, the willingness or access to the necessary infrastructure to practise as clinicians.

Challenges in interventional oncology

Several challenges exist in the field of interventional oncology that should be tackled to enable the practise of this discipline more effectively. These include a lack of sufficient relevant evidence of effectiveness, an appropriate clinical infrastructure and a robust quality assurance programme.

The need for data

Interventional oncology lacks the sound evidence base underpinning the practice of radiation oncology. Perhaps paradoxically, the rapid development of interventional radiological procedures in the field of oncology has impeded the establishment of the precise role of these methods of treatment in the oncological armamentarium. The majority of publications in interventional oncology focus on technological developments, such as radiofrequency or microwave ablation, irreversible electroporation, cryotherapy and radioembolization. Such scientific studies report the technical details of new procedures, document their technical success and safety, and compare them with each other. Although these issues are important, long-term outcome data and information on economic burden and quality of life are sparse. When comparisons with other methods of treatment are carried out, they are usually retrospective, or the patient cohorts are too different to enable valid comparison. There are several reasons for the relative paucity of substantial studies documenting the clinical effectiveness of interventional radiological techniques in oncology. The attraction of interventional radiologists to technology is one relevant factor, as many of their publications tend to focus on the influence of technological developments on the short-term outcomes of treatment rather than longer-term oncological results. However, more important is the fact that, in most cases, the patients being referred to the interventional radiologists are under the care of a separate clinical team or physician, who uses the interventional radiologist as a provider of a technical service. This makes comprehensive care more difficult, including the reliable follow up of patients. Furthermore, the referring service might regard its own method of treatment as 'mainstream' and the interventional techniques as adjunctive or as options of last resort, thereby only allocating patients who cannot be managed by other methods to the interventional radiologist. As a result, even retrospective comparisons might be difficult, because of differences in the patient populations treated by other oncological disciplines and by interventional radiologists.

A concerted effort is necessary to obtain reliable and substantial data on the outcomes of interventional radiological procedures in oncology. The funding of health care is under scrutiny in all developed countries and, inevitably, the investment decisions are based on the available scientific information. If interventional radiologists cannot produce the necessary evidence to support the procedures they wish to perform and believe to be of value to patients, this discipline is unlikely to establish itself as mainstream in the field of oncology. As well as having adverse consequences for the field of interventional oncology, this relative lack of substantial evidence in support of interventional radiological procedures will deprive patients from potentially beneficial and effective minimally invasive treatments.

The general thought is that only prospective randomized studies can provide acceptable evidence. Of course, when appropriate, such studies can be invaluable. However, these studies are expensive and time consuming, and are not always the most appropriate method of establishing the clinical effectiveness of a particular method of treatment.[77] Randomized controlled comparisons are particularly problematic when new surgical procedures are introduced.[78] Surgical procedures depend on the skills of the operator, are usually irreversible, and change constantly as new equipment and techniques are developed. In addition, use of a placebo is inappropriate, and adequate blinding is difficult to accomplish. These circumstances present problems in relation to operator participation and patient recruitment into randomized studies. Nonrandomized, prospective cohort comparison has other weaknesses, but can add complementary data with good external validity. Well-constructed, sophisticated registries are likely to be of great importance in interventional oncology. In a field of rapidly evolving technology, comparative effectiveness research is likely to be invaluable.[79] Patient-reported outcome measures and data from sophisticated registries are also likely to be particularly relevant to interventional radiological procedures. The field of interventional radiology is considerably disadvantaged in terms of collecting follow-up data; most departments are geared to intervention and not to long-term consultation and follow up by interventional oncologists. Interventional oncologists need to acquire the necessary infrastructure for full clinical practice and this should include data collection.

Clinical responsibility

The requirements for the effective practice of cancer medicine present a substantial number of challenges for interventional oncologists and for those who refer patients to them, as often interventional oncologists are not the primary clinicians caring for the patient. In the management of vascular diseases, it is possible for interventional radiologists, who choose to provide only a technical service, to function effectively in collaboration with vascular surgeons. However, it is difficult for interventional oncologists to provide optimum care without assuming primary clinical responsibility, with all of its ramifications, for the patients they treat; such responsibility is essential for the optimum care of patients with cancer. An interventional oncologist who is planning to perform an ablative procedure must take into account the impact of the procedure on the overall care of the patient and the integration of the procedure with other planned treatments. Without this level of integration with other members of the oncology team, decisions made in isolation could greatly disadvantage patients, leading to either unnecessary procedures or to complications that might

otherwise have been avoided. The interventional oncologist must be in a position to manage the complications of the procedure personally, rather than delegating this task to the referring physician. Patients should be followed up regularly, to assess the response to the procedure, to establish whether further treatment is needed, and to evaluate the overall value of the treatment to the patient. If follow-up assessment is delegated to others, information will be lost, delays could occur, and some potentially curable recurrent tumours might become untreatable by the time the interventional oncologist is made aware of them. In other patients, post-ablation tumour occurrence might be mistaken for persisting disease by other physicians and additional aggressive treatment might be offered.

Doctors in clinical specialties (surgical, radiation and medical oncology) caring for patients with cancer receive training in the principles and practice of oncology, which underpin their work. Such training enables them to communicate effectively with other specialists caring for the same patient and to put their role in the patient's treatment into a wider context. However, most interventional radiologists involved in cancer care have relatively limited clinical training, and little or no instruction in oncology. This deficit has to be rectified because interventional oncologists require the ability to communicate knowledgably with their colleagues and patients, as well as a clinical framework within which to do so, ideally within a multidisciplinary team. In the future, having some knowledge of the effects and mechanism of action of the various medications used to treat cancer will be even more important, as there is increasing evidence of interactions between some of these agents and the effects of interventional radiological techniques, affecting the rates of recurrence following percutaneous ablation,[80] or influencing complication rates or survival.[81]

The recognition of interventional radiology as a subspecialty of radiology by the General Medical Council in the UK and the award of specialty status by the American Board of Medical Specialties in the USA, has made it easier to incorporate knowledge of basic aspects of oncology into the training curricula of interventional radiologists, as well as to facilitate the assumption of full clinical responsibility by interventional radiologists.

The need for quality assurance

The field of radiation oncology has developed sophisticated programmes of quality assurance, which aim to provide consistency and assure safety of treatment.[82] Radiation oncology practice standards or quality assurance programmes exist in many countries and regions of the world. Support from medical physicists affiliated to departments of radiation oncology usually underpins the day-to-day quality assurance process. Good quality assurance programmes include a feedback mechanism so that the cause of any shortcomings can be addressed and corrected. Practice standards should be comprehensive, and although radiation oncology quality assurance programmes rightly have a major focus on ensuring accurate radiotherapy delivery, comprehensive programmes cover the whole care pathway, from the initial referral processes, through every step of decision-making, the delivery of care, the requisite staff, record keeping, and communication.[83,84] There needs to be rigour in treatment planning, the definition of the volumes of targets for treatment and avoidance, the planning process, the actual delivery of treatment, and follow-up strategy.

Quality assurance is not just about the equipment used. Being able to identify and accurately treat the target tissue is vital in radiotherapy and is just as important in interventional oncology. There is no consolation for a geographical miss of the target that could otherwise have been averted, no matter how sophisticated the technology used to deliver the treatment is. This is exemplified in the TROG 02.02 trial,[85] a multinational study evaluating the delivery of chemoradiation in patients with advanced-stage head and neck cancer, which required real-time quality assurance of the radiation treatment. Centres contributing small numbers of patients were found to have a considerably greater number of treatment deviations, and patients treated with poor quality plans were found to have a markedly reduced rate of locoregional control and overall survival.[85] Therefore, the field of interventional oncology requires robust methods of quality assurance to be developed, which should be adapted appropriately to the technology and methods of practice used in this discipline.[86]

The relationship with surgery

Surgery has a pre-eminent role in oncology, and many patients are cured as a result of successful surgical operations. Only surgery can ensure the total or partial removal of tissue containing a malignant tumour together with the lymph nodes draining it. Furthermore, several tumours in a single organ can be removed simultaneously during surgery. Moreover, histological examination of a surgical specimen can determine whether a neoplasm has been removed in its entirety and enables an assessment of risk factors and prognosis, thereby influencing recommendations for additional local or systemic treatment. Nevertheless, surgery also has some inherent limitations, which are inextricably linked with the above advantages. In particular, a substantial amount of normal parenchyma is lost during surgical operations. This problem might not be clinically significant in many cases; however, in some circumstances, it can have clinically important effects—for example, in patients with multiple tumours in a solitary kidney, such as some patients with von Hippel–Lindau disease, or in patients with recurrent hepatocellular carcinoma or several hepatic metastases affecting both lobes of the liver.

Interventional oncology enables the targeting and ablation of tumours with minimal loss of normal parenchyma. This process has substantial advantages when the disease is not limited to one part of an organ. For example, patients with metastases in both lobes of the liver, who require local treatment, often present a surgical challenge, whereas such disease might be treatable

with minimal loss of normal tissue using thermal ablation. Furthermore, most percutaneous ablations can be carried out under local anaesthesia, combined with intravenous sedation and analgesia, often in an outpatient setting or with an overnight stay in hospital. Indeed, the complications of interventional radiological procedures are generally fewer and less severe than those that follow equivalent surgical operations.

The relationship of interventional oncology to surgery can be complementary; however, in many situations, these approaches are directly competitive. For example, small renal tumours can be treated with percutaneous ablation with minimal loss of normal parenchyma and with very similar results to total or partial nephrectomy.[58,59] Some surgeons have raised doubts about the oncological efficacy of interventional radiological techniques on the basis of studies of histological findings showing a failure of ablation to destroy all malignant cells or to achieve the same tumour-free margins as surgery.[87] Ultimately, however, the effectiveness of interventional oncology must be judged on the local cure rate, overall survival and on the impact of the treatment on the patient's quality of life. It will be important to have a reliable database to guide evidence-based treatment recommendations that are supported by robust quality assurance procedures. Such data should record not only cancer outcomes, but also patient-reported quality of life and the overall economic burden of treatment.

The relationship with radiation oncology

In parallel with the advances in interventional oncology, ablation techniques are being developed in the field of radiation oncology. By way of example, SABR is emerging as the treatment of choice in patients with otherwise resectable lung tumours who are medically unsuitable for surgery. In appropriately selected patients, the results of SABR rival those of surgery and exceed those of percutaneous ablation.[88–91] Rigorous quality assurance, outcome measures and sophisticated data registries in SABR demonstrate the importance of such data in contributing to a robust evidence base for treatment.

Currently, no well-defined criteria are available to guide the selection of radiation therapy or percutaneous ablation for the treatment of a particular tumour. Sometimes the choice is obvious; for example, a patient with a small pulmonary tumour who has poor respiratory reserve and large emphysematous bullae would be more safely treated with radiotherapy than percutaneous ablation, because of the substantial risk of a life-threatening pneumothorax associated with the latter method.[72] Extensive work will need to be carried out during the next few years to define evidenced-based criteria for choosing between these methods of treatment, which should take into account the size, nature and location of tumours in various organs, and vulnerable adjacent structures. However, the choice should always be governed by the views expressed during careful discussion at a multidisciplinary meeting, taking into account the available expertise and patient choice, as well as the state of the lung (or other affected organ) itself.

Experimental and early clinical evidence suggests that, in the treatment of some conditions, the combination of radiotherapy and percutaneous ablation could have advantages over either technique alone.[92,93] This possibility is not surprising, as the underlying biological effects of either treatment method are different. Further research will help clarify this area.

Radiation oncology has always been dependent on imaging, as the targeting of tumours requires accurate localization of treatment. However, the reliance on imaging has increased considerably in recent years, as modern structural and functional methods of imaging are providing hitherto unprecedented detail regarding the location, structure and function of malignant neoplasms.[94] In this sense, interventional oncology and radiation oncology are converging; both disciplines require detailed imaging techniques to plan treatment and to assess its effectiveness, and can cure and palliate tumours, making it necessary to establish which modality should be used, or in which sequence, to achieve maximum patient benefit. New imaging methods might further increase the effectiveness of both radiation oncology and interventional oncology by providing detailed information relating to tumour activity. If interventional oncologists and radiation oncologists worked together, the spectrum of oncology covered by the two disciplines combined would be very extensive indeed.

The need for collaboration between radiation oncology and interventional oncology is undeniable, but what form this collaboration should take is debatable. In the long term, these disciplines could be brought closer by imaging, resulting in a new specialty.[95] Although this scenario is impractical in the immediate future, there will be substantial benefit from harnessing the expertise within these two disciplines. The techniques of delivering care are different. Interventional radiology has only recently acquired a character distinct from diagnostic radiology in the USA and the UK, and is not yet recognized as a subspecialty in most countries in Europe and in Australia. The curricula for training in interventional radiology in countries where a separate training track exists include a large number of vascular procedures, and separating the elements that apply to interventional oncology during training might be difficult. Furthermore, the number of interventional radiologists remains small compared with other specialties, making it difficult to offer 24-hour care in many medium-sized or small hospitals. This challenge will be even greater if this discipline were to be subdivided into vascular and oncological aspects. As in radiation oncology, however, the outcomes for patients requiring highly specialized treatment are likely to be better in specialized tertiary or quaternary care centres.

Currently, radiation oncology and interventional oncology are two disciplines that rely heavily on imaging and have similar treatment goals. The two fields complement each other and have a lot to gain from a close association. Collaboration could be facilitated by joint appointments, with interventional oncologists being employed part-time in departments of radiation

oncology, or by a commitment to work together in prominent centres. For interventional oncologists, joint appointments will have the additional advantage of providing them with access to the infrastructure they need to practise as clinicians rather than technicians. Facilities and support staff for outpatient clinics, and ward support for inpatients, would transform the pattern of practice of interventional oncology. In addition, encouraging interventional oncologists to participate in multidisciplinary meetings will facilitate integration and joint research projects. Such integration might also accelerate the adaptation of some of the mature planning and quality assurance techniques used routinely in radiation oncology to the needs of interventional oncology.

Organizations and professional colleges in which both radiology and radiation oncology are represented, including the Royal College of Radiologists (RCR) and the Royal Australian and New Zealand College of Radiologists (RANZCR), should explore methods of bringing interventional oncologists and radiation oncologists closer together. The RCR[96] and the RANZCR[97] have faculties of Radiology and Radiation Oncology (called 'Clinical Oncology' in the case of the RCR). These faculties could collaborate to create a curriculum for training specialists in interventional oncology, which should include a basic knowledge of radiotherapy and chemotherapy, as well as essential clinical knowledge relating to oncology. Such knowledge would not be sufficient for interventional radiologists performing procedures in patients with cancer to function as independent oncologists who can prescribe chemotherapy or radiotherapy; however, it would enable them to put the procedures they perform in a wider context and to communicate better with the patients they treat.

Conclusions

Interventional oncology is a promising new discipline, which offers exciting procedures that can cure, control or provide palliative care for several malignant conditions. However, this discipline is challenged by the lack of comprehensive relevant evidence of effectiveness, a robust quality assurance framework and an appropriate infrastructure for clinical practice. Whereas the evidence base underpinning radiation oncology is robust and has developed over decades, interventional oncology does not have this luxury, making comparative effectiveness research a vital platform for gathering evidence. Furthermore, radiation oncology relies on rigorous quality assurance at every level of delivery. For interventional oncology, there is an urgent need to gather evidence of clinical effectiveness and develop methods of quality assurance. Adopting the principles used by radiation oncologists for this purpose will help accelerate the establishment of similar methods within interventional oncology. As in radiation oncology, quality assurance and evidence gathering in interventional oncology must be embedded in multidisciplinary team management, to facilitate decision-making and the integration of care, and to extend treatment options. In the current environment of escalating health-care costs and of the consequent need to base the availability of methods of treatment on robust outcome measures, the relevant considerations are similar for both disciplines. Interventional oncologists and radiation oncologists should emphasize outcomes that reflect the importance of local tumour control as well as the overall economic burden of treatment and quality of life measures that are important to patients and to the health system at large. Therefore, a close collaboration between the two disciplines will provide highly important potential gains for both patients and practitioners.

Review criteria

A formal literature search to identify articles for inclusion in this Review was not performed owing to the wide subject area covered. We searched Google Scholar for articles published on the topic of ablation of renal tumours to identify articles highlighting differences between interventional oncology and surgery. The search terms used were "partial nephrectomy", "renal tumours", "radiofrequency", and "cryotherapy". This Review includes a summary of the authors' work and knowledge based on reading the oncology and interventional radiology literature. Knowledge gained from regular attendance at conferences, workshops, and other national and international meetings was also included.

1. Fairchild, A. *et al.* Palliative thoracic radiotherapy for lung cancer: a systematic review. *J. Clin. Oncol.* **26**, 4001–4011 (2008).
2. Skladowski, K. *et al.* Randomized clinical trial on 7-day continuous accelerated irradiation (CAIR) of head and neck cancer—report on 3-year tumor control and normal tissue toxicity. *Radiother. Oncol.* **55**, 101–110 (2000).
3. Rose, P. *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N. Engl. J. Med.* **340**, 1144–1153 (1999).
4. Kenny, L., Peters, L., Rodger, A., Barton, M. & Turner, S. Modern radiotherapy for modern surgeons: an update on radiation oncology. *ANZ J. Surg.* **72**, 131–136 (2002).
5. Kenny, L. M., Peters, L. J., Barton, M. & Milross, C. Radiotherapy—a leap forward in cancer care. *Cancer Forum* **37**, 42–46 (2013).
6. Coles, C. E., Moody, A. M., Wilson, C. B. & Burnet, N. G. Reduction of radiotherapy-induced late complications in early breast cancer: the role of intensity-modulated radiation therapy and partial breast irradiation. Part II—radiotherapy strategies to reduce radiation-induced late effects. *Clin. Oncol.* **17**, 98–110 (2005).
7. Bucci, M. K., Bevan, A. & Roach, M. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. *CA Cancer J. Clin.* **55**, 117–134 (2005).
8. Delaney, G., Jacob, S., Featherstone, C. & Barton, M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* **104**, 1129–1137 (2005).
9. Jacob, S., Wong, K., Delaney, G. P., Adams, P. & Barton, M. B. Estimation of an optimal utilisation rate for palliative radiotherapy in newly diagnosed cancer patients. *Clin. Oncol. (R. Coll. Radiol.)* **22**, 56–64 (2010).
10. Dotter, C. T. & Judkins, M. P. Transluminal treatment of arteriosclerotic obstruction: description of a new technic and a preliminary report of its application. *Circulation* **30**, 654–670 (1964).
11. Molyneux, A. J. *et al.* International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* **366**, 809–817 (2005).
12. Katsanos, K. *et al.* Systematic review and meta-analysis of thermal ablation versus surgical nephrectomy for small renal tumours. *Cardiovasc. Intervent. Radiol.* **37**, 427–437 (2014).

13. Becker, G. J., Katzen, B. T. & Dake, M. D. Noncoronary angioplasty. *Radiology* **170**, 921–940 (1989).
14. Chabbert, V. *et al.* Midterm outcomes of thoracic aortic stent-grafts: complications and imaging techniques. *J. Endovasc. Ther.* **10**, 494–504 (2003).
15. García-Pagán, J. C. *et al.* Early use of TIPS in patients with cirrhosis and variceal bleeding. *N. Engl. J. Med.* **362**, 2370–2379 (2010).
16. Kee, S. T. *et al.* Superior vena cava syndrome: treatment with catheter-directed thrombolysis and endovascular stent placement. *Radiology* **206**, 187–193 (1998).
17. Marcy, P. Y. *et al.* Superior vena cava obstruction: is stenting necessary? *Support. Care Cancer* **9**, 103–107 (2001).
18. Nicholson, A. A., Ettles, D. F., Arnold, A., Greenstone, M. & Dyet, J. F. Treatment of malignant superior vena cava obstruction: metal stents or radiation therapy. *J. Vasc. Interv. Radiol.* **8**, 781–788 (1997).
19. Rozenblit, A. *et al.* Endovascular repair of abdominal aortic aneurysm: value of postoperative follow-up with helical CT. *AJR Am. J. Roentgenol.* **165**, 1473–1479 (1995).
20. Struk, D. W., Rankin, R. N., Eliasziw, M. & Vellet, A. D. Safety of outpatient peripheral angioplasty. *Radiology* **189**, 193–196 (1993).
21. Swanson, K. L. *et al.* Bronchial artery embolization: experience with 54 patients. *Chest* **121**, 789–795 (2002).
22. Uyeda, J. W., LeBedis, C. A., Penn, D. R., Soto, J. A. & Anderson, S. W. Active hemorrhage and vascular injuries in splenic trauma: utility of the arterial phase in multidetector CT. *Radiology* **270**, 99–106 (2014).
23. Farrell, T. A. & Hicks, M. E. A review of radiologically guided percutaneous nephrostomies in 303 patients. *J. Vasc. Interv. Radiol.* **8**, 769–774 (1997).
24. Bettmann, M. A., Perlmutt, L., Finkelstein, J., Meyerovitz, M. F. & Richie, J. P. Percutaneous placement of soft, indwelling ureteral stent. *Radiology* **157**, 817–818 (1985).
25. Lang, E. K. *et al.* Placement of metallic stents in ureters obstructed by carcinoma of the cervix to maintain renal function in patients undergoing long-term chemotherapy. *AJR Am. J. Roentgenol.* **171**, 1595–1599 (1998).
26. Van Arsdalen, K. N., Pollack, H. M. & Wein, A. J. Ureteral stenting. *Semin. Urol.* **2**, 180–186 (1984).
27. Ferrucci, J. T., Mueller, P. R. & Harbin, W. P. Percutaneous transhepatic biliary drainage: technique, results and applications. *Radiology* **135**, 1–13 (1980).
28. Mueller, P. R. *et al.* Biliary stent endoprostheses: analysis of complications in 113 patients. *Radiology* **156**, 637–639 (1985).
29. Gibson, R. N. *et al.* Percutaneous transhepatic endoprosthesis for hilar cholangiocarcinoma. *Am. J. Surg.* **156**, 363–367 (1988).
30. Adam, A., Yeung, E., Chetty, N., Roddie, M. & Benjamin, I. S. Self-expandable stainless steel endoprostheses for the treatment of malignant bile duct obstruction. *AJR Am. J. Roentgenol.* **156**, 321–325 (1990).
31. Laméris, J. S. *et al.* Malignant biliary obstruction: percutaneous use of self-expandable stents. *Radiology* **179**, 703–707 (1991).
32. McKeown, B. J., Wong, W. L. & Adam, A. True single-stage percutaneous insertion of Wallstent biliary endoprostheses. *Minim. Invasive Ther. Allied Technol.* **3**, 257–260 (1994).
33. Stoker, J. & Lameris, J. S. Complications of percutaneously inserted biliary Wallstents. *J. Vasc. Interv. Radiol.* **4**, 767–772 (1993).
34. van Delden, O. M. & Lameris, J. S. Percutaneous biliary drainage and stenting for palliation of malignant bile duct obstruction. *Eur. Radiol.* **18**, 448–456 (2008).
35. Dumonceau, J. M. *et al.* Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* **44**, 277–298 (2012).
36. Adam, A. *et al.* Palliation of inoperable esophageal carcinoma: a prospective randomized trial of laser therapy and stent placement. *Radiology* **202**, 344–348 (1997).
37. Adam, A., Morgan, R., Ellul, J. & Mason, R. C. A new design of the esophageal Wallstent endoprosthesis resistant to distal migration. *AJR Am. J. Roentgenol.* **170**, 1477–1481 (1998).
38. Song, H. Y. *et al.* Covered, expandable esophageal metallic stent tubes: experiences in 119 patients. *Radiology* **193**, 689–695 (1994).
39. Watkinson, A. F., Ellul, J., Entwisle, K., Mason, R. C. & Adam, A. Esophageal carcinoma: initial results of palliative treatment with covered self-expanding endoprostheses. *Radiology* **195**, 821–827 (1995).
40. Ellul, J., Watkinson, A. F., Khan, R., Adam, A. & Mason, R. C. Self-expandable metal stents for the palliation of dysphagia due to inoperable oesophageal carcinoma. *Br. J. Surg.* **82**, 1678–1681 (1995).
41. Saxon, R. R. *et al.* Malignant esophageal obstruction and esophagorespiratory fistula: palliation with a polyethylene-covered Z-stent. *Radiology* **202**, 349–354 (1997).
42. Costamagna, G. *et al.* Prospective evaluation of a new self-expanding plastic stent for inoperable esophageal strictures. *Surg. Endosc.* **17**, 891–895 (2003).
43. May, A., Hahn, E. G. & Ell, C. Self-expanding metal stents for palliation of malignant obstruction in the upper gastrointestinal tract. *J. Clin. Gastroenterol.* **22**, 261–266 (1996).
44. Cheung, H. Y. & Chung, S. C. Covered metal stent for tumor obstruction of efferent loop recurrence after gastrectomy. *Surg. Endosc.* **11**, 936–938 (1997).
45. Pinto, I. T. Malignant gastric and duodenal stenosis: palliation by peroral implantation of a self-expanding metallic stent. *Cardiovasc. Intervent. Radiol.* **20**, 431–434 (1997).
46. Yates, M. R., Morgan, D. E. & Baron, T. H. Palliation of malignant gastric and small intestinal strictures with self-expanding metal stents. *Endoscopy* **30**, 266–272 (1998).
47. Binkert, C. A., Jost, R., Steiner, A. & Zollikofer, C. L. Benign and malignant stenoses of the stomach and duodenum: treatment with self-expanding metallic endoprostheses. *Radiology* **199**, 335–338 (1996).
48. Ruiz, P. L. *et al.* New intraluminal bypass tube for management of acutely obstructed left colon. *Dis. Colon Rectum* **38**, 1108–1109 (1995).
49. Rousseau, H. *et al.* Self-expandable prostheses in the tracheobronchial tree. *Radiology* **188**, 199–203 (1993).
50. Inchingolo, R. *et al.* Tracheobronchial stenting for malignant airway disease: long-term outcomes from a single-center study. *Am. J. Hosp. Palliat. Care* **30**, 683–689 (2013).
51. Goldberg, S. N., Gazelle, G. S., Compton, C. C., Mueller, P. R. & Tanabe, K. K. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. *Cancer* **88**, 2452–2463 (2000).
52. Narayanan, G. Irreversible electroporation for treatment of liver cancer. *Gastroenterol. Hepatol.* **7**, 313–316 (2011).
53. Lee, E. W. *et al.* Advanced hepatic ablation technique for creating complete cell death: irreversible electroporation. *Radiology* **255**, 426–433 (2010).
54. Liang, P. *et al.* Ultrasound guided percutaneous microwave ablation for small renal cancer: initial experience. *J. Urol.* **180**, 844–848 (2008).
55. Cannon, R., Ellis, S., Hayes, D., Narayanan, G. & Martin, R. C. Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. *J. Surg. Oncol.* **107**, 544–549 (2013).
56. Brace, C. L. Radiofrequency and microwave ablation of the liver, lung, kidney, and bone: what are the differences? *Curr. Probl. Diagn. Radiol.* **38**, 135–143 (2009).
57. Breen, D. J. *et al.* Percutaneous cryoablation of renal tumours: outcomes from 171 tumours in 147 patients. *BJU Int.* **112**, 758–765 (2013).
58. Olweny, E. O. *et al.* Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. *Eur. Urol.* **61**, 1156–1161 (2012).
59. Takaki, H. *et al.* Radiofrequency ablation versus radical nephrectomy: clinical outcomes for stage T1b renal cell carcinoma. *Radiology* **270**, 292–299 (2014).
60. Ferakis, N., Bouropoulos, C., Granitsas, T., Mylona, S. & Poulias, I. Long-term results after computed-tomography-guided percutaneous radiofrequency ablation for small renal tumors. *J. Endourol.* **24**, 1909–1913 (2010).
61. Psutka, S. P. *et al.* Long-term oncologic outcomes after radiofrequency ablation for T1 renal cell carcinoma. *Eur. Urol.* **63**, 486–492 (2013).
62. Krokidis, M. *et al.* Percutaneous radiofrequency ablation of small renal tumours in patients with a single functioning kidney: long-term results. *Eur. Radiol.* **23**, 1933–1939 (2013).
63. Hur, H. *et al.* Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. *Am. J. Surg.* **197**, 728–736 (2009).
64. Elias, D. *et al.* Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. *Eur. J. Surg. Oncol.* **26**, 763–769 (2000).
65. Pawlik, T. M. *et al.* Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann. Surg. Oncol.* **10**, 1059–1069 (2003).
66. Leung, E. Y., Roxburgh, C. S., Leen, E. & Horgan, P. G. Combined resection and radiofrequency ablation for bilobar colorectal cancer liver metastases. *Hepatogastroenterology* **57**, 41–46 (2010).
67. Salem, R. *et al.* Treatment of unresectable hepatocellular carcinoma with use of ^{90}Y microspheres (TheraSphere): safety, tumor response, and survival. *J. Vasc. Interv. Radiol.* **16**, 1627–1639 (2005).
68. Stubbs, R. S., Cannan, R. J. & Mitchell, A. W. Selective internal radiation therapy (SIRT) with ^{90}Yttrium microspheres for extensive colorectal liver metastases. *Hepatogastroenterology* **48**, 333–337 (2001).
69. Sharma, R. A. *et al.* Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J. Clin. Oncol.* **25**, 1099–1106 (2007).
70. Stuart, K. Chemoembolization in the management of liver tumors. *Oncologist* **8**, 425–437 (2003).

71. de Baere, T. *et al.* Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. *Radiology* **240**, 587–596 (2006).
72. Simon, C. J. *et al.* Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology* **243**, 268–275 (2007).
73. Yasui, K. *et al.* Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. *Radiology* **231**, 850–857 (2004).
74. Gadaleta, C. *et al.* Radiofrequency ablation of 40 lung neoplasms: preliminary results. *AJR Am. J. Roentgenol*. **183**, 361–368 (2004).
75. Wolf, F. J. *et al.* Microwave ablation of lung malignancies: effectiveness, CT findings, and safety in 50 patients. *Radiology* **247**, 871–879 (2008).
76. Wang, H. *et al.* Thoracic masses treated with percutaneous cryotherapy: initial experience with more than 200 procedures. *Radiology* **235**, 289–298 (2005).
77. Rawlins, M. De Testimonio: on the evidence for decisions about the use of therapeutic interventions. *Clin. Med*. **8**, 579–588 (2008).
78. Lassen, K., Høye A. & Myrmel, T. Randomised trials in surgery: the burden of evidence. *Rev. Recent Clin. Trials* **7**, 244–248 (2012).
79. Scott, I. A. Comparative effectiveness research—the missing link in evidence-informed clinical medicine and health care policy making. *Med. J. Aust*. **198**, 310–312 (2013).
80. Ahmed, M. *et al.* Combined radiofrequency ablation and adjuvant liposomal chemotherapy: effect of chemotherapeutic agent, nanoparticle size, and circulation time. *J. Vasc. Interv. Radiol*. **16**, 1365–1371 (2005).
81. Jin, Y. *et al.* Radiofrequency ablation combined with systemic chemotherapy in nasopharyngeal carcinoma liver metastases improves response to treatment and survival outcomes. *J. Surg. Oncol*. **106**, 322–326 (2012).
82. Williamson, J. F. *et al.* Quality assurance needs for modern image-based radiotherapy: recommendations from 2007 interorganizational symposium on "quality assurance of radiation therapy: challenges of advanced technology". *Int. J. Radiat. Oncol. Biol. Phys*. **71** (Suppl.), S2–S12 (2008).
83. The Faculty of Radiation Oncology (FRO), The Royal Australian and New Zealand College of Radiologists (RANZCR), Australian Institute of Radiography (AIR), & The Australasian College of Physical Scientists and Engineers in Medicine (ASPSEM). *Radiation Oncology Practice Standards* [online], http://www.radiationoncology.com.au/supporting-docs/ranzcr-standards.pdf (2011).
84. Radiation Oncology Practice Standards. *Supplementary guide* [online], http://www.radiationoncology.com.au/supporting-docs/ranzcr-standardsguide.pdf (2011).
85. Peters, L. J. *et al.* Critical Impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J. Clin. Oncol.* **28**, 2996–3001 (2010).
86. Crocetti, L., de Baere, T. & Lencioni, R. Quality improvement guidelines for radiofrequency ablation of liver tumours. *Cardiovasc. Intervent. Radiol.* **33**, 11–17 (2010).
87. Rendon, R. A. *et al.* The uncertainty of radio frequency treatment of renal cell carcinoma: findings at immediate and delayed nephrectomy. *J. Urol*. **167**, 1587–1592 (2002).
88. Loo, B. W. Stereotactic ablative radiotherapy (SABR) for lung cancer: what does the future hold? *J. Thorac. Dis*. **3**, 150–152 (2011).
89. Haasbeek, C. J., Lagerwaard, F. J., Slotman, B. J. & Senan, S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. *J. Thorac. Oncol*. **6**, 2036–2043 (2011).
90. Senthi, S., Lagerwaard, F. J., Haasbeek, C. J., Slotman, B. J. & Senan, S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol*. **13**, 802–809 (2012).
91. Senthi, S., Haasbeek, C. J., Slotman, B. J. & Suneth, S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. *Radiother. Oncol.* **106**, 276–282 (2013).
92. Dupuy, D. E. Radiofrequency ablation followed by conventional radiotherapy for medically inoperable stage I non-small cell lung cancer. *Chest* **129**, 738–745 (2006).
93. Jain, S. K., Dupuy, D. E., Cardarelli, G. A., Zheng, Z. & DiPetrillo, T. A. Percutaneous radiofrequency ablation of pulmonary malignancies: combined treatment with brachytherapy. *AJR Am. J. Roentgenol*. **181**, 711–755 (2003).
94. Dawson, L. A. & Jaffray, D. A. Advances in image-guided radiation therapy. *J. Clin. Oncol*. **8**, 938–946 (2007).
95. Zietman, A. Image-targeted oncology: a 21st century specialty waiting to be born. Presented at The Royal College of Radiologists Clinical Oncology Annual Meeting 2013.
96. RCR. *The Royal College of Radiologists* [online], www.rcr.ac.uk (2014).
97. RANZCR. *The Royal Australian and New Zealand College of Radiologists* [online], www.ranzcr.edu.au (2014).

Author contributions

Both authors researched the data for the article, provided substantial contributions to discussions of content, wrote the article, and reviewed and/or edited the manuscript before submission and after peer review.