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Intensity Modulated Radiotherapy (IMRT)

A Guide for Commissioners

An NRIG Technology sub-group Report

- November 2009.

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Tim Cooper
Associate Director – Radiotherapy
National Cancer Action Team

timcooper@nhs.net

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Executive Summary

- This document sets out the rationale supporting the requirement for Intensity Modulated Radiotherapy (IMRT) in the treatment of patients with cancer.
- IMRT is a high precision form of radiotherapy. It conforms the shape and dose of the radiation precisely to the volume of tumour tissue that needs to be treated.
- The ability to precisely shape radiation dose to the tumour target means that the amount of radiation received by critical organs and normal tissues surrounding the tumour can be reduced or avoided. This reduces the toxic side-effects of radiotherapy. By reducing side-effects, higher radiation doses can be given, which may lead to increased tumour control rates in patients with certain cancers.
- IMRT therefore offers the following benefits:
  - Improved quality of life for patients, from reduced side-effects
  - Potential to decrease medication costs, from reducing the need to manage long-term, serious toxicities.
  - Potential to improve cancer control rates, from possible dose escalation.
- These advantages have lead to its widespread adoption across Europe and North America where it has become the standard of care for many indications.
- The National Cancer Peer Review Standards for radiotherapy will require IMRT as a radiotherapy service option in a least one centre per radiotherapy network.
- A review of the available evidence was carried out by the joint radiotherapy professionals' body, the Radiotherapy Development Board (RDB), to identify which patients could most benefit from IMRT. The use of IMRT was recommended in a subset of patients with the following cancers: Head & neck, Breast, Prostate, Paediatrics, CNS, Pancreas.
- Calculations based on current demographics have shown that about 30% of patients having cancers treated with radiotherapy could benefit from IMRT.
- The resources required to undertake IMRT include specialist software for calculating the precise distribution of doses to tumours, hardware for use in quality assurance procedures, specialist radiation delivery equipment and appropriately trained staff.
- Many of the resource issues have been addressed by national programmes. Following recent Department of Health (DH) initiatives, 97% of radiation equipment in England is now IMRT ready. The National Cancer Action Team (NCAT) will shortly launch a programme to provide national staff training and support.

- Revenue funding for service provision has lagged behind equipment provision; nationally, forward planned IMRT is currently provided to about 10% of patients which matches our prediction. However inverse planned IMRT is only delivered to about 2% or patients rather than to the estimated 24% who would benefit from it.

In conclusion, it is recommended IMRT is adopted as the standard of care within radiotherapy services for those patients that would most benefit and that funds should therefore be made available to support the operational service costs required.

Introduction

The purpose of this document is to provide information to healthcare commissioners on the advanced radiotherapy technology, Intensity Modulated Radiotherapy (IMRT). It sets out the rationale for IMRT to be the standard of care for many radiotherapy patients, describing the benefits to patients with cancer and the resources required to achieve it. The document also provides a summary of current evidence and recommendations for the need and management of IMRT.

The Role of Radiotherapy

Radiotherapy is an essential curative treatment (second only to surgery) which is involved in the management of 40% of those patients who are cured of cancer. It is expected that this figure will rise with the implementation of new technologies such as IMRT. It has been estimated that the addition of radiotherapy to other treatments improves 5 years survival by 16%, overall for all comers [1]. This should be compared with the 5 year survival contribution of cytotoxic chemotherapy which has been estimated at 2% overall; this is because the diseases in which chemotherapy is most effective for cure are rare [2].

Policy Background

The National Radiotherapy Advisory Group (NRAG) report was published in 2007 [3]. It reviewed the background of the longstanding under-investment in radiotherapy and set out a plan to develop a world class service. It followed on from previous studies internationally indicating the requirements for radiotherapy services. A particularly important review was the ESTRO-QUARTS report which showed that in 2004 England (with Slovenia, Poland and the Czech Republic) had approximately 50% of the capacity which that model predicted [4]. By contrast, in Sweden, France and Belgium the availability of megavoltage therapy units was 90% of the QUARTS estimate [4]. The NRAG report therefore confirmed the findings of other analyses that there was a very significant under-provision of radiotherapy capacity in England [3]. This conclusion was accepted by ministers [3].

In planning a response, many services have focused on access and waiting times targets but the report also endorsed the technological development of radiotherapy. The overall aim of the NRAG report was to develop world class radiotherapy and it was envisaged that within 10 years 50% of patients would be treated by imaged guided 4-dimensional adaptive radiotherapy (see technology sub-group report [5]). This means that the radiotherapy plan is adjusted during the course of treatment as the tumour responds or according to movement of the tumour during treatment. The first step to developing this is to implement IMRT.

Even before the NRAG report there had been ongoing centrally funded capital investment in radiotherapy equipment over a total of 10 waves investing a total £170 million. A strategic decision was made early on that all equipment should be IMRT capable and at present 97% of linear accelerators in the NHS in England are capable of delivering IMRT and have a software licence to do so. Thirty percent of machines are equipped to undertake image guided radiotherapy (IGRT). The obstacles to developing the service have been the revenue consequences attached to training and to staff time for outlining planning and quality assurance. Most of the services which have been developed have been funded by research or soft funds and the service is only available to about 2% of NHS radiotherapy patients overall. Nevertheless, the policy intent that this service should

be developed is clear. £200 million was identified in the Cancer Reform Strategy (2008) to develop radiotherapy [6].

Cost Effectiveness of Radiotherapy

Radiotherapy is a relatively cheap and effective treatment that consumes a low proportion of the total cancer budget amounting to 5% in both England [6] and Sweden [7]. It is wrongly perceived as an expensive service. This is because linear accelerators now cost approximately £1.5 million and need to be sited in a bunker costing over £0.5 million. There are also staff costs which, as in other health related activity, dominate long-term financial planning, accounting for 54% of the costs of radiotherapy [8]. However surgery, for example, also has substantial capital and staff costs and it is important to examine the costs and cost effectiveness of the modality. An international review of the literature published in 2008 concluded that radiotherapy offered very good value for money with a 21 fraction course of treatment costing 3239€ +/- 566€ [8] The real increase in cost over the last 15 years was estimated to be only 5.5%. This updated the earlier report by Barton et al who estimated the cost per life year gained (excluding skin cancer) as $7186 [1], well within the cut-off of £20-30,000 per QUALY used by NICE.

Early results from the National PbR reference cost work for radiotherapy support the published data, that radiotherapy is a cheaper intervention than both surgery and chemotherapy when the full cost base is calculated across the life cycle of the resource.

Technological Development

Radiotherapy has seen a succession of technological developments with the successive introduction of high energy machines, initially cobalt and then linear accelerators. Treatment planning has evolved from simple hand planning, with X-ray films, to CT based planning which has then evolved into 3-D conformal treatment. In general the improvements have been deemed to be self-evident although small studies have often been done to support the case for change.

In 1996 the Swedish Council on Technology Assessment in Health Care [9] estimated that developing radiotherapy technology would account for approximately 10% greater cancer cure rates, of which 4% would be attributable to technical developments including radiotherapy delivery. IMRT will deliver a large part of this predicted improvement in cure rates, but has not been widely taken up in the UK so far.

What is IMRT?

Conventional radiotherapy as practiced in the 1980's used rectangular fields aimed from 3 or 4 directions to treat tumours located by CT scan. In the 1990's conformal radiotherapy became established as the standard of care. This used the same applied fields but they were shaped with lead blocks or multi-leaf collimators (MLC^S) to limit irradiation of surrounding normal tissues.

IMRT represents a completely different approach to treatment planning. The tumour target must be identified and outlined on every slice of the CT scan. All relevant healthy tissue structures must also be outlined as the aim is to produce a complex plan which minimises dose to them whilst giving a homogeneous dose to the tumour. This is achieved by using multiple beamlets of radiotherapy to build up the dose within the tumour volume.

IMRT planning can be done conventionally by applying and adjusting beamlets from a chosen direction. This is the approach used to achieve a homogenous dose in selected patients with breast cancer. It is a simpler technique and is called forward planned IMRT.

By contrast, inverse planned IMRT is planned using a computer which independently selects the best options for treatment to meet a series of constraints set to limit doses to surrounding normal tissues. The options available can be constrained into a class solution or a completely novel approach can be adopted by the planning computer. The plan is then reviewed by staff and repeatedly adjusted and improved to meet the dose constraints imposed by normal tissue tolerance.

IMRT is resource intensive in both the use of clinician time for outlining and the use of clinician, physics and radiographer time for complex planning. The plan must be reviewed in detail by the clinician and then adjusted to optimise the dose distribution. There is also much more detailed quality assurance to ensure that the correct dose is given to the correct part of the patient with millimetre precision. This is necessary because margins are much tighter in this treatment technique and because the treatment delivery process is more complex.

However, once the planning and quality assurance have been performed, the actual treatment times are similar to conventional treatment, particularly for complex head and neck cases. This is because the machine is computer controlled during treatment rather than radiographers having to repeatedly enter the room to set up and match a complex programme of multiple field arrangements. Moreover with further recent advances in software it is possible to deliver IMRT even more swiftly thereby facilitating throughput of patients.

The Advantages of IMRT

IMRT is a radiotherapy dose delivery system which conforms the dose to the target volume. This can be achieved even if the target is concave and ‘hugs’ radiation-sensitive healthy tissue e.g. spinal cord. It is possible to reduce doses to normal tissue and therefore the radiotherapist’s ultimate aim is achieved namely to treat the tumour to the highest dose possible and minimise exposure of normal tissues. There is good evidence that tumours are dose responsive, i.e., that as the dose increases so does the cure rate. This has been shown in dose escalation studies in a number of malignancies and prostate cancer is a particularly well researched example.

The toxicity of radiotherapy also depends on dose and on the volume of healthy tissue irradiated. Short term toxicity (otherwise known as ‘acute’ toxicity) can be reduced by eliminating the unnecessary irradiation of normal tissues. For example soreness of the mouth and throat can be reduced by better targeted treatment.

The effects of long term radiation damage (otherwise known as ‘late’ toxicity) can be catastrophic and may take 10, to 20, to 30 years to appear [10]. There is clear long term evidence of fatal late effects on, for example, the heart in the treatment of breast cancer where a 5% increase in non-breast cancer deaths has been shown at 20 years [11]. It has also been shown that the risk is linked to the volume exposed and the dose to which it is treated [11]. Similar data are now emerging for stroke risk after irradiation of the carotid arteries in the treatment of head and neck cancer [12].

It is clear that reducing the volume of normal tissue treated and dose to which it should be exposed should be a long term aim of modern radiotherapy planning procedures. There is therefore a strong theoretical basis for promoting the use of IMRT on the basis of improved tumour response and decreased fatal and serious late normal tissue side effects over decades. This argument has been accepted by commissioners world-wide and it is estimated that 30-50% of patients are treated with IMRT in North America and much of Europe.

Risks of IMRT

The major disadvantage of IMRT is the much more widespread distribution of low doses within parts of the body which would be spared with conventional treatments. This arises because multiple beams must all enter and leave the body and this increases the amount of low dose radiation. In addition, for some treatments the beam on time is longer and there is increased leakage from the machine head and collimator which varies with manufacturer and beam energy [13]. Low dose effects have contributed to unexpected lung toxicity but this problem is now better understood. Of much greater concern is the question of increased risk of second cancers occurring decades after treatment [13]. This is particularly a worry in younger patients with a good prognosis, especially children [14, 15]. Predicting these risks is a complex problem as much of the data on which calculations are based arise from non-medical exposures at relatively low dose, including the atomic bomb data. Depending on the model used, other authors have argued that IMRT reduces the risk of second cancers both in adults [16] and children [16, 17].

Evidence Base for IMRT

Two major reviews have been published [18, 19]. These show that a large number of patients have been accrued into clinical trials but many of these have not yet been reported. The timescales are such that most aim to study acute side effects and tumour response. The published data are summarised as follows:

Head and neck cancer

There is convincing evidence that IMRT provides improved dosimetry ('conformality') compared to 3-dimensional conformal radiotherapy (3D-CRT). For example, IMRT has been shown to produce dosimetrically superior plans in head and neck cancer compared to conventional planning techniques. Reduction in xerostomia (dry mouth) has been proven in three randomised clinical trials, including one performed in the UK, by reducing the volume of parotid glands irradiated to no more than about a third of that delivered to the tumour. There are several other potential advantages including safe dose escalation, improved dose homogeneity (i.e. reduced 'hot spots' itself reducing side effects) and reduced irradiation of other radiation-sensitive organs (spinal cord, brainstem, optic nerves, mucosa etc). IMRT may also be faster than conventional conformal techniques for this patient group with consequent savings of linac time.

Breast cancer

There is evidence from two randomised trials that IMRT can be used to reduce the toxicity caused by the inherent dose inhomogeneity (i.e. 'hot spots') of conventional tangential post-operative breast radiotherapy. IMRT may also be useful in reducing cardiac and lung irradiation in selected cases. The 3D assessment of the dose distribution from standard tangential radiotherapy should now be a standard procedure by routine CT planning, so that IMRT can be offered to patients with a high degree of dose inhomogeneity (which

carries an increased risk of long term late effects such as breast pain and distortion). It has been shown that two thirds of breast radiotherapy patients would achieve an improved dose distribution with a simple forward planned solution. It is not clear from trials so far published that all these patients would benefit clinically so we have used a conservative estimate of one third of patients elsewhere in this document.

Prostate cancer

Prostate cancer trials have shown that a higher dose will lead to higher rates of local control and cure. This has been clearly demonstrated for intermediate and high-risk prostate cancer. There is strong evidence that, when using the previous standard dose of 64-68 Gy, shaping of the radiation fields to the prostate and seminal vesicles using conformal radiotherapy resulted in a reduction in side-effects such as rectal disturbance, proctitis and bleeding from 15-18% to 5-8%. Subsequent randomised trials using higher doses have shown a significant improvement in local tumour control using higher doses between 74-78 Gy. However, these trials also showed that a 2-fold increase in the side-effects of treatment. The rectum, lying close to or within the concavity of the prostate target, can now be spared by IMRT and the radiation dose can then be escalated to much higher doses i.e. 81 Gy, with side-effects limited to approximately 3-5%. Thus the sequential application of advanced techniques has improved tumour control and reduced serious side effects. This will translate into improved patient outcomes..

Paediatric tumours

English radiotherapy lags lamentably behind in implementing advanced techniques for children's cancers. Irradiation of normal tissue in children causes a significant impact on their future development, both in physical deformity and in intellectual development. Brain tumours are the commonest malignancy and there is no reason to irradiate non-tumour bearing developing normal brain where it can be avoided by technical innovation. IMRT will permit a reduction in late effects in the developing brain and at other sites where radiotherapy is required for cure. IMRT should be routinely available to children as an option until such time as proton therapy can be offered in the UK rather than referral abroad: the funding of this option emphasises the importance placed nationally on the long term effects of radiotherapy on growing children. A ministerial statement on the tendering process for developing proton therapy in England was published in August 2009.

Other indications

There is also evidence to support the use of IMRT in locally advanced pancreatic cancer, non-small cell lung cancer, and adult CNS tumours. There are also obvious dosimetric advantages in clinical scenarios where the tumour is close to an organ at risk.

Consent Issues and patient information

IMRT is therefore well established for a number of indications. The GMC requires that patients are told of all alternatives for their treatment and it is now clear that this should be discussed as an option for patients with advanced head and neck cancer, selected cases of breast cancer and many cases of prostate cancer. There are a wide range of other indications and indeed some patients may be essentially untreatable without an IMRT solution. Patients are becoming increasingly well informed and will reasonably expect to be offered IMRT for some indications.

Evidence of this is shown by the fact that members of the Royal College of Radiologists Clinical Oncology Patient Liaison Group formally confirmed their strong support for the implementation of IMRT in at least one radiotherapy centre per cancer network for all

appropriate patients by 2012; it is anticipated that similar support will be given by SCoR PLG members at their next meeting.

Demand for IMRT

IMRT is a technique that can deliver improved dose distributions compared to conventional techniques and it should be available to all clinical oncologists when deciding the optimum treatment for their patients.

There will be clinical scenarios, such as locally advanced head and neck cancer, where a clear advantage has been shown for many patients; there will be sites where IMRT should be implemented routinely, e.g. improved dose distribution for some cases of breast cancer and dose escalation for prostate cancer; and there will be sites where individual difficulties in planning determine the choice of IMRT, e.g. certain brain tumours and tumours close to the spinal cord.

Table 1 uses data from a survey of radiotherapy usage in 2005 by the Royal College of Radiologists [20]. IMRT is currently only relevant to the 53% of patients being treated radically for cure and they received 80% of all fractions prescribed. Onto these data have been mapped indications for IMRT and the proportion of patients likely to benefit. The proportion of all fractions which should be given as IMRT has then been calculated. Breast cancer is identified separately as it can be treated with a forward planned (less resource intensive) solution as outlined above. As the disease is so common and as radiotherapy has a pivotal role in its management, this would account for about 9% of all radiotherapy fractions. Inverse planned IMRT should be used for a variety of indications and the disease sites identified for early implementation amount to about 25% of all radiotherapy fractions; prostate cancer dominates these indications because it is so common. Overall it is estimated that about 33% of fractions should be delivered using IMRT. These are global national estimates and demand should be based on local data developed with clinicians.

Table 1: Estimate of percentage of radically treated patients likely to benefit from IMRT and consequent proportion of all fractions as IMRT.

Tumour site	% of all RT fractions	% pts who benefit	% all fractions as IMRT	
			Forward Planned	Inverse Planned
Breast	30%	30%	9%	-
Prostate	16%	80%		13%
Gynaecological	5%	20%		1%
H + N	8%	80%		6%
CNS	3%	60%		2%
Other sites	10%	20%		2%
		Total	**9%**	**24%**
		Grand Total	**33%**	

Cost Effectiveness of IMRT

The additional treatment costs of IMRT have been assessed in a UK study in which it was shown that compared to conformal radiotherapy treatment time changed little, but there was an increase in planning time [21]. A recent study from Europe claimed that costs increased by about 30% because of slower delivery [22] but did not compare similar patients as the earlier study had done[21]. To estimate incremental cost effectiveness the gains must be quantitated in terms of QUALYs. There have been some North American studies but these were based on reimbursement rates rather than true additional costs. Work in progress on prostate cancer using UK data is awaited. It is expected that IMRT will be able to provide benefit well within the cut-off of £20-30,000 per QUALY used by NICE largely because a reduction in the costs of treating severe late effects.

NICE undertook an initial scoping consideration to IMRT. This included discussion with professional bodies, clinical leads and national policy leads. Their conclusion was that this is not a new treatment (having evolved from conformal radiotherapy); NICE therefore recognised that it was appropriate for guidance to be developed by the professional groups. Also as 4D adaptive radiotherapy including IMRT was also a recommendation within both CRS and NRAG, this was in fact national policy, as de facto agreement had already been provided by government. It should therefore be taken forward in the NHS, led by NCAT and the National radiotherapy Implementation Group (NRIG) Technology sub-group, and offered to those patients who may benefit from it.

Development of Tariff

Currently, there is no additional NHS tariff for IMRT. This acts as a disincentive to implementation. There is a national shortage of trained staff, particularly physicists and therapy radiographers. This is difficult to address without the requisite tariff.

A system of tariff that reflects the additional complexity of advanced IMRT is required. Such a tariff system, acknowledging the added quality provided by IMRT, will allow trusts to plan a properly resourced radiotherapy service based on clinical need. This is being developed within the National PbR Tariff programme, but will not be available until 2012 at the earliest. In the interim, a local agreement (based on nationally recognised practice) is required.

National Cancer Action Team Training programme and support measures

In order to facilitate the delivery of IMRT, the National Cancer Action Team; through NRIG, are developing and funding a national training programme for IMRT. This programme will be based on the concepts of the colorectal TME programme of whole team training and local support for delivery. Tenders for training will be sought in autumn 2009.
This programme recognises the clinical delivery requirements that services have set out, and supports the development of this clinical procedure to a high standard.
Additional tools to support this change include:

- A generic business case to support the commissioning requirements. This ensures a common approach to setting up and delivering IMRT. It also seeks to reassure commissioners that this service development is both national supported and that the requirements are credible.
- A dosimetric audit to allow QA of the delivery systems, thus reassuring safety.
- A grandfathering process to support developing services.

- Peer review measures that drive the change from within
- A publication of the evidence for IMRT by the Radiotherapy Development Board in Journal of Clinical Oncology – Staffurth et al.
- This guide to IMRT for commissioners, setting out policy, to assist a clear (non clinical) understanding of the issues.

Cancer Peer Review Measures

Revised National Cancer Peer Review measures for radiotherapy are now out for consultation; they include a new section on the availability and quality assurance of IMRT provision. IMRT should be available in at least one radiotherapy centre in each network.

Conclusion

This document lays out the rationale for the implementation of IMRT as the standard of care for many radiotherapy patients. At least one third of breast cancer patients should be offered the relatively simple technique of forward planned IMRT to improve dose distribution and decrease the risk of distressing long term side effects in the conserved breast: this will apply to about 9% of all radiotherapy fractions delivered as the disease is so common. A range of other indications (e.g. head and neck cancer) will account for the use of inverse planned IMRT for about 24% of all radiotherapy fractions, making a total with breast of about 33% of treatments.

It is recommended IMRT is adopted as the standard of care within radiotherapy services for those patients that would most benefit and that funds should therefore be made available to support the operational service costs required.

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