Radiation oncology : A clinical update from the north west cancer centre

Ulster Med J 2019;**88(2):**91-97

Grand Rounds

Radiation Oncology: A Clinical Update from The North West Cancer Centre.

Walls GM[1,2], Lyons C[1], Jellett LJ[1], Evans R[1], Bedair A[1], Brady D[1], McLaughlin LM[1], Reilly E[1], Reilly A[1], McAleer JJ[3,4], Stewart DP[1].

Accepted: 1st March 2019
Provenance: externally peer reviewed

HISTORY OF THE NORTH WEST CANCER CENTRE

Following an announcement in 2008 from Mr Michael McGimpsey, Minister for Health, Social Services and Public Safety, a business case was developed for a new Cancer Centre based at Altnagelvin Area Hospital. It was designed to provide radiotherapy and chemotherapy treatment for a population of around 500,000 in the North and West of Northern Ireland. The Irish government agreed to provide revenue and capital funding to facilitate the provision of radiotherapy-only services for the population of most of County Donegal. In May 2011, Mr Edwin Poots, then Minister for Health, Social Services and Public Safety, approved funding for the North-West Cancer Centre (NWCC), including this cross-border service. The plan represented a successful collaboration between the governments of Northern Ireland and the Republic of Ireland.

Fig 1. The North West Cancer Centre, Altnagelvin Area Hospital

The Centre is the second radiotherapy centre in Northern Ireland and is designed to address an anticipated increase in cancer incidence. It has also improved access to cancer treatment for a population which previously had to travel 2-4 hours for radiotherapy in Belfast, Galway or Dublin. The NWCC has three linear accelerators (Linacs) for delivering radiotherapy and space for a fourth. Curative and palliative treatments are offered and emergency treatment is available. From the outset, emerging technical radiotherapy planning techniques have been incorporated into the NWCC. It is one of the few UK centres to integrate MRI-based simulation, image artefact removal methods and iterative cone-beam CT scanning to visualize anatomy on the Linac. These techniques facilitate safer delivery of radiotherapy by reducing potential toxicity and maximising tumour control. Less common tumours are better managed centrally at the regional Cancer Centre at Belfast City Hospital - contribution of NWCC to managing these tumours will be modest.

Currently, curative-intent radiotherapy is available for patients with cancer of the breast, prostate, bladder, rectum, head/neck and haematological systems. Local patients treated in Belfast who have unscheduled admissions at NWCC receive integrated care, in part due to regional electronic Oncology records. Systemic therapies such as chemotherapy and immunotherapy are delivered in the same building and a new Macmillan Centre for holistic and supportive care has been located nearby. An active clinical trials portfolio is planned. Working together in multi-professional teams is facilitated by grouped office space for physicians from Clinical and Medical Oncology and Palliative Medicine, medical physics and radiographers, administrative and managerial staff. Over 200 staff are now employed at the Centre, and the building's architects won national and international prizes for its design (Figure 1). On 9th May 2017, the NWCC was officially opened by His Royal Highness, Prince Charles and Camilla, Duchess of Cornwall.

INTRODUCTION TO RADIOTHERAPY

Radiotherapy is the use of ionising radiation as treatment for benign and malignant disease. Approximately 40% of patients diagnosed with cancer will receive radiotherapy during the course of their illness.[1] Increasing cancer incidence, improved understanding of tumour biology and advances in engineering have led to improvement in radiotherapy treatment in recent decades. The complex therapies available have contributed to improved survival and quality of life and have enabled

[1]The North West Cancer Centre, Western Health & Social Care Trust
[2]Centre for Cancer Research & Cell Biology, Queen's University Belfast
[3]Cancer Centre Belfast City Hospital, Belfast Health & Social Care Trust

Correspondence to Dr Gerard Walls

E-mail: g.walls@qub.ac.uk

Clinical Oncologists to reduce early and late radiation side-effects. This article is intended to update clinical colleagues on the optimal radiotherapy management of some common cancers.

GENERAL RADIOTHERAPY PRINCIPLES

Mode of Action

"Ionising radiation" refers to moving particles which interact with atoms to cause liberation of electrons. In radiotherapy, the resulting chemical reactions induce lethal damage in cells by a variety of mechanisms (Table 1). The underlying principle is that cancer cells are less effective in repairing damage than normal cells and are therefore more susceptible to radiation. The dose of radiation required to kill all the tumour cells in a cancer would cause intolerable toxicity if given as a single treatment. This is mitigated by dividing the total dose into smaller (often daily) treatments (fractions), over a period of weeks. This causes cumulative damage to the tumour, whilst allowing the surrounding normal tissue time to repair. Several different types of ionising radiation are used to treat malignancy, although photons and electrons predominate in routine clinical practice. Radiation is usually delivered to tumours from outside the body (external-beam radiotherapy; EBRT), but sealed and unsealed radioactive sources may also be directly applied to a tumour inside the body (brachytherapy).

Table 1

Types of cellular damage[2]

Type of Damage	Frequency (per cell per Gray)
DNA-protein cross-links	1000
Altered DNA bases	3000
Single-strand DNA breaks	1000
Double-strand DNA breaks	20-40

Radiotherapy Planning

Photon (X-ray) beams are generated by a Linac (Figure 2) and directed toward the target in the patient as defined by the Clinical Oncologist. Cross-sectional imaging from a dedicated non-diagnostic CT scanner is required for accurate identification of this target in advance. To reduce the risk of causing damage in adjacent organs, careful planning is given to the direction, shape and intensity of the beams. Diagnostic imaging and, increasingly, planning MRI scans are carried out in the treatment position to assist definition of the target volume(s) and organs at risk (OARs). This process, known as radiotherapy planning, usually takes 2-3 weeks; however, the planning time required varies with the treatment indication and complexity (Table 2).

Delivery of Radiotherapy

When a treatment plan has been finalised, therapeutic radiographers coordinate the delivery of radiotherapy, with input from clinicians, medical physicists and clinical engineers as required. A session of radiotherapy takes approximately 15 minutes to deliver. Replicating the treatment planning position takes several minutes, and delivering the fraction usually takes up to five minutes. The delivery process does not involve undue noise, light, heat or pain. Patients do not pose any risk as a radiation hazard and are unlikely to experience significant immediate side-effects, and treatment is usually delivered on an outpatient basis.

Dose of Radiotherapy

Until recently, most patients treated with potentially curative (radical) radiotherapy for cancer were treated with conventional dose-fractionation schedules, delivering a dose of 1.8-2Gy daily over many weeks. Recently, there has been a move towards shorter, hypo fractionated schedules that allow delivery of a biologically equivalent dose of radiation over a shorter period. This, in a more pronounced form, is the basis of stereotactic ablative body radiotherapy (SABR), which is increasingly used in the treatment of early lung and prostate cancer and in the treatment of oligometastatic disease. Palliative treatments to improve symptoms are delivered as a limited number of fractions of radiotherapy, with larger daily doses than conventional treatment (although not as large as SABR).

Table 2

Indications for radiotherapy

Indication	Intention of Treatment
Radical	To eradicate potentially curable cancer
Adjuvant	To reduce risk of locoregional recurrence after radical surgery
Neoadjuvant	To reduce tumour volume prior to radical surgery
Palliative	To reduce symptoms of incurable cancer (metastatic or locally advanced)
Emergency	To prevent acute clinical deterioration, usually from an incurable cancer

The risk of late toxicity in normal organs can be reduced by optimising the radiation dose distribution using two advanced technologies:

Linacs capable of intensity-modulated radiotherapy (IMRT) produce beams of X-rays that vary in shape dynamically whilst X-rays are being delivered. The most modern Linacs produce IMRT from hundreds of angles in rapid succession in a single circular plane, in a technique called volumetric arc therapy (VMAT).

Imaging hardware built into modern Linacs is used to verify target location relative to the original treatment plan each day, known as image-guided radiotherapy (IGRT). High-quality patient alignment on the treatment couch by radiographers means the lowest radiation exposure possible is received by adjacent organs, as modelled using complex software

during the planning process. When satisfied with the patients' position using measurements and wall-mounted lasers, manual and automated cone beam CT imaging processes confirm the target location with high precision.

Fig2. A modern linear accelerator (Model shown is Varian TrueBeam©)

Unlike systemic anti-cancer therapies, radiotherapy side-effects are restricted to the anatomical region being irradiated - except for fatigue. The early side-effects of treatment (onset within 3 months of completing treatment) tend to occur towards the end of a course of radiotherapy and can continue for weeks to a few months. Clinicians regularly assess radiotherapy reactions during and after treatment and tailor supportive treatments accordingly. Guidance is available online from the NI Cancer Network (NICAN) for other doctors who encounter the early side-effects. [3] Late side-effects of radiotherapy (apparent after three months to many years) are identified during later follow-up. Although they are becoming less frequent as techniques improve, sometimes side-effects occur many years after treatment (e.g. valvular heart disease, myelitis, urethral stricture and radiation-induced malignancy). As more people are cured of their cancer this is assuming greater significance.

PROSTATE CANCER TREATMENT PRINCIPLES

Background

The management of localised prostate cancer with radiotherapy is based on the risk of relapse, as inferred from histopathology, tumour markers and imaging – Gleason grade, baseline PSA and MRI of pelvis. [4] As well as surgical and conservative options, localised disease is considered for radiotherapy to the prostate gland. For many patients, radical radiotherapy provides cure rates comparable to prostatectomy, in excess of 80%. [5] Of note, the entire prostate gland is targeted due to the malignant 'field change' seen in the prostate. Alternatives to radiotherapy may include active surveillance, radical (robotic) prostatectomy and brachytherapy.

Conventionally, prostate radiotherapy comprised 7-8 weeks of daily treatment, totalling a dose of 74-78Gy. Clinical trials have recently introduced shorter equivalent, hypo-fractionated schedules of 60Gy over a period of 4 weeks.[6,7,8] In selected high-risk cases, 78Gy delivered over 8 weeks remains the preferred strategy. Prophylactic treatment of the at-risk pelvic lymph nodes may also be offered.[7]

The common early side-effects of treatment are fatigue, urinary frequency, nocturia, dysuria, diarrhoea and rectal irritation. Later side-effects include altered bowel habit, rectal bleeding, and sexual dysfunction. Pelvic fistulae are rarely seen. Patients with intermediate- and high-risk localised prostate cancer treated with radical radiotherapy may also be offered concomitant androgen-deprivation therapy, which also affects sexual function (in addition to other potential toxicities) and can be employed in the both neoadjuvant and adjuvant settings.

Example Case

Mr A, 63 years old, was diagnosed with intermediate-risk, localised prostate adenocarcinoma (Gleason 3+4, T2a N0 M0, initial PSA 9ng/ml). Apart from mild lower urinary tract symptoms, his medical history was limited to bilateral total hip replacements.

Referral

The Urologist presented his case at the weekly cancer multidisciplinary meeting (MDM), and Mr A was seen by the Clinical Oncologist one week later. After discussion of the treatment options, the patient expressed a preference for EBRT (60Gy in 20 fractions over 4 weeks) rather than implanted radioactive seeds or surgery and LHRH agonist subcutaneous implants were arranged via his family doctor.

Radiotherapy Clinic

Mr A visited the planning clinic 8 weeks later, allowing time for the cytostatic effects of ADT to develop. PSA was satisfactory at <0.01ng/ml. The rationale for radiotherapy was discussed in detail with Mr A, illustrating this on the radiology system with the patient's own baseline anatomy. Baseline symptom assessment was documented and supportive medications were prescribed. He was counselled on bladder-filling and bowel preparation by a therapeutic radiographer working in the same clinic.

Planning Scan

Mr A had a CT planning scan later that afternoon, following a first attempt at bladder and bowel preparation. This was performed in the radiotherapy delivery position with the patient supine and flat on the scanner assisted by head and knee rests, and without IV contrast (lymph nodes not for treatment). Automated artefact-removal techniques removed metallic hip prostheses artefact (Figure 3), an increasingly important aid, given the aging demographic of the population diagnosed with cancer. Mr A subsequently had MRI imaging carried out in the treatment position which was co-registered with his planning CT facilitating optimal interpretation of the pelvic anatomy (Figure 4, not Mr A).

Treatment Planning

The Oncologist delineated the target volumes and OARs on tablets (Figure 5) using the fused images. Additional

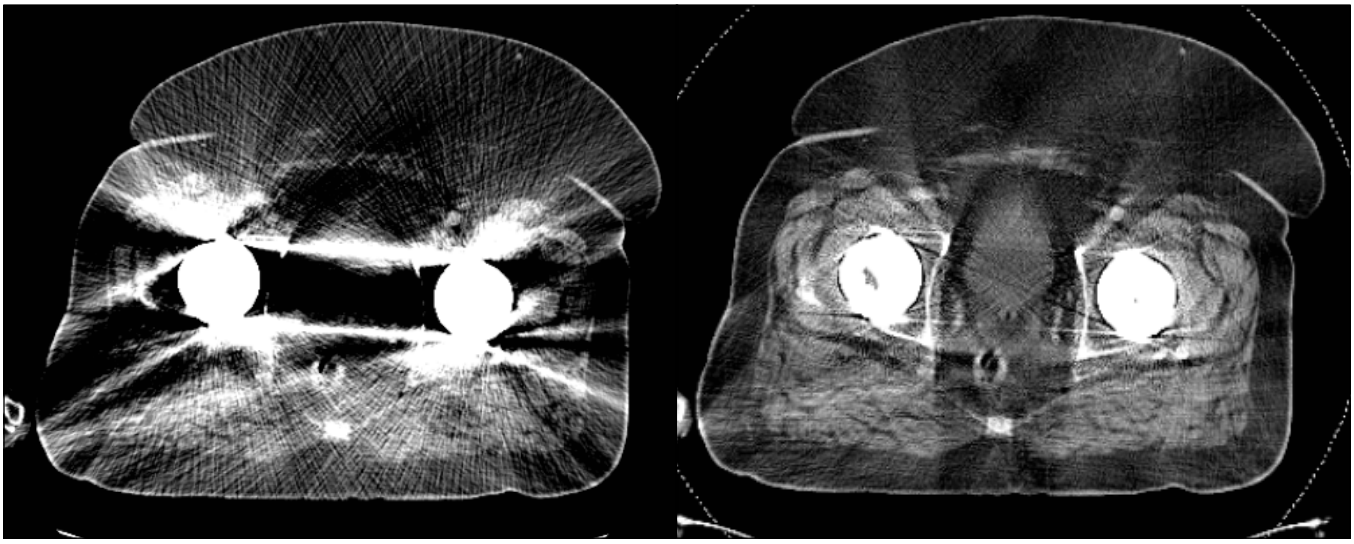

Fig 3. Axial appearances of the pelvis before (left) and after (right) the dual-energy CT artefact removal technique, with significantly clearer images of the bladder and bowel when artefact from the metallic hips is removed.

diagnostic-quality monitors at the workstation enabled the clinician to simultaneously refer to a planning atlas and the patient's electronic medical record. The physics team determined the optimal beam arrangements to achieve the dose prescribed by the Oncologist in their shared workspace. Finalised plans were forwarded to the treatment radiographers.

Treatment Delivery

The location of the prostate, between the bladder and the rectum, prevents complete sparing of normal organ irradiation. Standardisation of bladder filling and rectal emptying prior to treatment allows more accurate targeting the prostate and reduces potential side-effects. Integrated cone-beam CT scanning carried out immediately prior to each treatment facilitated daily review of bladder, rectum and prostate size and position. [9] Within 40 minutes of arriving in the building, Mr A had usually completed his VMAT-delivered fraction. He was reviewed by the treating team weekly to assess symptoms and early toxicity. Clinical documentation and onward referrals to radiotherapy nurses or physiotherapists was completed electronically, as were discharge letters to the family doctor.

Follow-up

Six weeks following treatment, Mr A was reviewed in the radiotherapy department. The urology team were updated regularly and Mr. A remained on regular follow-up with the Oncology team. One year after completion of radical radiotherapy, Mr A stopped androgen deprivation therapy and reported no significant sequelae from radiotherapy and had maintained an excellent biochemical response to treatment.

BREAST CANCER TREATMENT PRINCIPLES

Background

Wide local excision and post-operative whole-breast radiotherapy is equivalent to mastectomy for early breast cancer in terms of local recurrence. [10] Adjuvant radiotherapy in this setting aims to kill any undetectable malignant cells that were not removed at surgery. If clinicopathological features justify post-operative chemotherapy, this is given prior to radiotherapy.

Historically, whole-breast radiotherapy comprised 5 weeks of daily treatment, totalling a dose of 50Gy. Clinical trials have introduced hypo fractionated schedules of 40Gy in 15 fractions. [11] In selected cases, an additional 'boost' dose is given to the tumour bed. [12] Similarly, ipsilateral supraclavicular fossa (SCF), internal mammary chain and post-mastectomy chest wall irradiation are reserved for specific higher-risk scenarios.

The common early side-effects of treatment are fatigue, skin reaction and mild breast swelling. The late side-effects include altered breast texture, skin changes (telangiectasia and discolouration), pneumonitis and cardiac toxicity (left-sided cancers).

Example Case

Mrs B was a 61-year-old post-menopausal woman with a symptomatic left-sided breast cancer (T1 N2 M0, grade II ductal cancer, (ER-positive, PR-positive HER2-negative), who was referred for consideration of adjuvant therapy following wide local excision and axillary node clearance.

Referral

The breast MDM consensus was that chemotherapy, radiotherapy and endocrine therapy should be offered to reduce the risk of recurrence. The rationale for these adjuvant therapies was discussed in depth when Mrs B was seen jointly by the Oncologist and Breast Care Nurse.

Radiotherapy Clinic/Planning Scan

Mrs B attended radiotherapy planning clinic just before her fifth chemotherapy cycle. Having provided written consent,

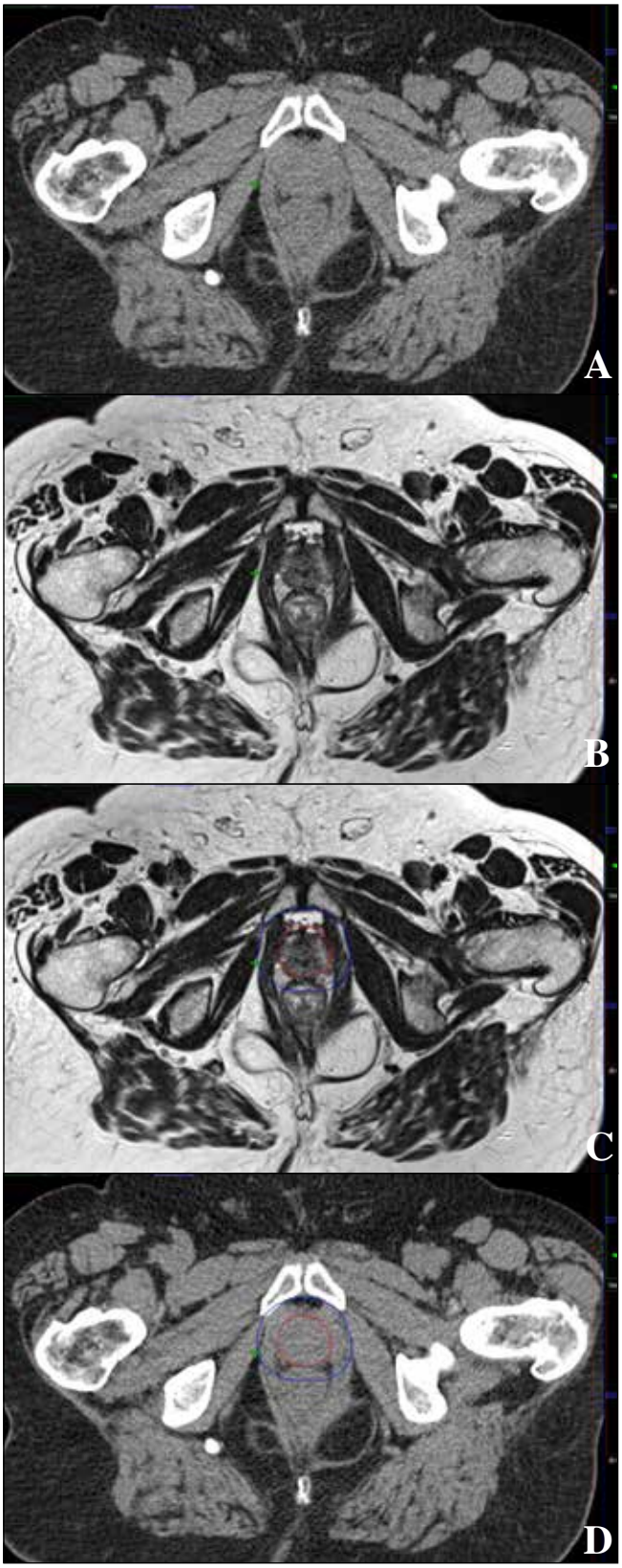

Fig 4. poorly visualised pelvic anatomy on CT scans (A) such as target organs like prostate (red) plus a margin of safety (blue) and organs at risk such as bowel (purple) may be better visualised on MRI images (B) so Oncologists use the latter to define organs (C) and transfer these to the CT images using CT-MRI co-registration (D).

three pin-point reference tattoos were applied (over the sternum and in the mid-axillary line on each side) to aid positioning during treatment, after her planning CT scan.

Treatment Planning

All breast radiotherapy in the NWCC is planned based on individually delineated target volumes, which is a significant enhancement over our earlier practice of conventional field-based planning. The Oncologist delineated the breast and nodal volumes with reference to international contouring guidelines. A Consultant Radiologist with a special interest in breast radiology joined the Oncologist to agree the defined SCF volume prior to generation of the optimal individualised treatment plan.

Fig 5. Contouring workstation

Treatment Delivery

Treatment began 3 weeks after her final chemotherapy cycle. Each day the patient was placed in the treatment position and imaged immediately prior to each fraction. Automated image matching was performed using bone landmarks and surgical clips (in the tumour bed), to optimise alignment. In-vivo dosimetry allowed verification of the delivered dose. Mrs B reported no side-effects and she tolerated her endocrine treatment without difficulty.

Follow-up

At twelve weeks following treatment completion Mrs B had no evidence of radiotherapy-related toxicity and proceeded to the self-directed aftercare programme.

LUNG CANCER TREATMENT PRINCIPLES

Background

Radical radiotherapy is offered to patients diagnosed with stage I-III non-small cell lung cancer (NSCLC) or limited stage small cell lung cancer (SCLC) who have a good performance status. Thoracic radiotherapy is the treatment of choice for patients who decline, or are unsuitable for surgery and is combined with concurrent chemotherapy if possible. [13]followed by central collection, checking, and reanalysis of updated individual patient data. Results from trials were

combined using the stratified log-rank test to calculate pooled hazard ratios (HRs Advances such as stereotactic ablative radiotherapy (SABR) have comparable results to surgery for stage I lung cancer. [14] Radiotherapy can also control symptoms and disease progression in incurable lung cancer, which comprises over half of new cases of lung cancer diagnosed in Northern Ireland. [15] Radiotherapy may also be delivered to the area of the chest where a tumour was resected (adjuvant radiotherapy) or to the whole brain prophylactically.

Lung radiotherapy schedules vary greatly, lasting between 2 and 6 weeks in the radical setting. A smaller number of fractions (eg one to 13 daily treatments) is particularly effective for palliation of haemoptysis, pain, cough or dyspnoea. SABR is reserved for smaller and more peripherally located tumours (eg 54-55Gy in 3-5 fractions).

The common early side-effects of lung radiotherapy include fatigue, skin reaction, oesophagitis and cough, with some patients experiencing breathlessness due to pneumonitis after 3-4 months. Less common, late side-effects include long-term breathlessness (due to lung fibrosis), cardiac toxicity and, rarely, spinal cord damage (myelitis). Late side-effects are rare with the dose-fractionation schedules used in palliative radiotherapy.

Example Case

Mr C (67 years old) was diagnosed with a stage IIIA adenocarcinoma of the right lung following investigation of new dyspnoea and weight loss of 6 kg. Molecular tests for EGFR mutation, ALK rearrangement and PDL-1 expression were negative.

Referral

Following discussion between the Oncologists and Surgeons at the central lung MDM, radical chemoradiotherapy was advised. He was seen by the Clinical Oncologist, who discussed the diagnosis, staging and treatment options. The patient consented to 55Gy in 20 fractions over four weeks to commence with cycle 3 of chemotherapy.

Planning Scan

Having embarked on chemotherapy, Mr C proceeded to radiotherapy planning. A 4D-planning CT scan was carried out. This CT scan uses motion-tracking technology to track the tumour in all phases of the respiratory cycle.

Treatment Planning

The lung tumour target volume was delineated in all phases of respiration. Taking account of organ motion during each respiratory cycle allows more accurate targeting of the tumour and minimises the treated volume. The treatment plan was approved at peer review within two weeks of the planning scan.

Treatment Delivery

Cone-beam CT was performed daily to facilitate visualisation of the tumour and appropriate matching of the plan. Accurate localisation of the tumour increases adherence to the prospectively modelled doses, including the OARs such as the oesophagus, which is particularly important in patients with baseline weight loss. Progressive improvement of tumour-associated consolidation during treatment led to increasing difficulty in matching and prompted re-planning, which was achieved within one week. During treatment, Mr C reported only mild oesophagitis responsive to sucralfate and a proton pump inhibitor.

Follow-up

At subsequent appointments there were no symptoms of radiation-induced toxicity, and follow-up imaging demonstrated excellent clinical response.

CONCLUSIONS

Radiotherapy was first delivered at NWCC on 30th November 2016. The establishment of the North West Cancer Centre has brought the latest advances in radiotherapy to its population, previously disadvantaged by distance from established centres, for the treatment of genitourinary, breast, lower gastrointestinal, lung head/neck cancer and haematological cancers. At the time of publication, almost 1500 patients have received radiotherapy at NWCC.

Radiotherapy is a fast-changing field of medicine, and there has been much development over the last decade; treatment planning and delivery is becoming more complex and the absolute numbers of patients receiving radical and palliative treatment increases. The ultimate aim of treatment is that these advances translate into tangible improvements in overall survival and quality of life for patients living with – and beyond – cancer.

REFERENCES

1. Ahmad SS, Duke S, Jena R, Williams M V, Burnet NG. Advances in radiotherapy. *BMJ*. 2012;**345**:e7765.
2. Joiner MC, van der Kogel A. Basic clinical radiobiology. 4th ed. Abingdon, Oxon: CRC Press; 2009.
3. Northern Ireland Cancer Network (NICAN). Guidance for patients who become ill whilst receiving radiotherapy or within 6 weeks of radiotherapy. Belfast: NICaN; 2014. Available from: http://nican.hscni.net/content/guidance-management-patients-who-become-ill-whilst-receiving-radiotherapy-or-within-6-weeks. Last accessed March 2019.
4. D'Amico A, Whittington R, Malkowicz S, Schultz D, Blank K, Broderick GA, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;**280(11)**:969–74.
5. Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, *et al*. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys*. 2004;**58(1)**:25–33.
6. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, *et al*. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;**17(8)**:1047–60.

7. Roach M, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, *et al*. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1994;**28(1)**:33–7.

8. Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, *et al*. Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. *Radiother Oncol*. 2007;**84(2)**:121–7.

9. de Crevoisier R, Bayar MA, Pommier P, Muracciole X, Pêne F, Dudouet P, et al. Daily versus weekly prostate cancer image-guided radiotherapy: Phase 3 multicenter randomized trial. *Int J Radiat Oncol Biol Phys*. 2018; **102(5)**:1420-29.

10. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, *et al*. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;**347(16)**:1233–41.

11. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, *et al*. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. 2008; **371(9618)**: 1098-107.

12. Bartelink H, Horiot JC, Poortmans P, Struikmans H, van den Bogaert W, Barillot I, *et al*. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med*. 2001;**345(19)**:1378–87.

13. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, *et al*. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non–small-cell lung cancer. *J Clin Oncol*. 2010;**28(13)**:2181–90.

14. Bryant AK, Mundt RC, Sandhu AP, Urbanic JJ, Sharabi AB, Gupta S, *et al*. Stereotactic body radiation therapy versus surgery for early lung cancer among US veterans. *Ann Thorac Surg*. 2018;**105(2)**:425–31.

15. Queen's University Belfast: Research Centres: Northern Ireland Cancer Registry. Cancer in Northern Ireland 2015: Lung Cancer. Belfast; NI Cancer Registry: 2016. Available from: http://www.qub.ac.uk/research-centres/nicr/FileStore/OfficialStats2015/FACTSHEETS/Filetoupload,746050,en.pdf#search=lung%20cancer. Last accessed March 2019.