Radiotherapy update

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This is the sixth in a series of articles examining recent developments in cancer

In the narrowest sense radiotherapy is a treatment almost exclusively used in managing cancer and based on the use of ionising radiation. In practice, however, the scope of the subject is broad (box 1) as management decisions relating to cancer must be made in the context of a thorough appraisal of the tumour and patient. Tumours are characterised by histogenesis and morphology, and, increasingly, molecular and genetic analyses are improving the precision and prognostic power of histopathology.¹⁻³ Assessment of patients must incorporate not only a thorough general medical examination but investigation with both established and developing radiological techniques, which can provide sensitive assessments of extent of disease and may soon be able to give information such as tumour blood flow,⁴ cell membrane turnover,⁵ proliferative capacity, or degree of oxygenation.⁶

Radiotherapy is used for about half of the 200 000 patients who develop cancer in the United Kingdom each year.⁷ It has a curative role in two thirds of patients and a palliative role in the remainder (box 2). Increasingly, management of cancer also involves surgery and chemotherapy.⁸ For many cancers the appropriate balance of treatments is still being evaluated, and audit and clinical trials are particularly important in view of the speed and frequency with which treatment advances are brought into clinical practice. Among the problems compounding the difficulties of treating cancer is the need for medical and psychological support for coincidental or treatment related problems and for the anxiety and stress experienced by patients and their relatives at the prospect of a life threatening illness.⁹ In the United Kingdom radiotherapists are often also responsible for chemotherapy, and the breadth of management responsibility has led to the renaming of the specialty as clinical oncology.

Clinical role

The role of radiotherapy for particular tumours is determined partly by the average radiosensitivity of the tumour relative to adjacent normal tissues and partly by the probability that the tumour is localised (box 2). Thus radiotherapy has a curative role in cancers of the head and neck; gynaecological tumours, especially

Box 1—Functions covered by specialty of radiotherapy

General medical management of the cancer patient
Clinical and radiological assessments of disease stage
Curative high dose radiotherapy
Palliative radiotherapy
Chemotherapy
Hormone therapy
Biological therapies
Symptom control
Psychological support
Audit
Clinical research
Management
Public education
Teaching and training

Box 2—Clinical roles of radiotherapy

Curative as sole treatment for:

- Head and neck cancers
- Cancer of the cervix
- Seminomas
- Hodgkin's disease and non-Hodgkin's lymphoma
- Bladder cancer
- Early prostate cancer
- Early lung cancer
- Anal and skin cancers
- Medulloblastoma and some other brain tumours
- Thyroid cancer

Component of multimodality curative treatment:

- Breast cancer
- Rectal cancer
- Soft tissue sarcomas
- Advanced head and neck cancers
- Whole body radiotherapy before marrow transplants

Palliative radiotherapy:

- Pain especially bone metastases
- Bleeding—for example, haemoptysis, haematuria
- Spinal cord compression
- Brain metastases
- Venous or lymphatic obstruction

carcinoma of the cervix; early lymphomas including Hodgkin's disease; seminoma of the testis; early carcinoma of the prostate; and locally advanced cancers of the bladder. Additionally a small proportion of localised bronchogenic carcinomas can be cured with radiotherapy, and it has a role complementary to surgery in treating breast cancer, rectal cancer, and sarcomas. Improvements in radiotherapy, as with other medical practices, must be judged in terms of therapeutic ratio. Most of the biological effects of radiation are secondary to cytotoxicity and are determined partly by the physical characteristics of the radiation, partly by dose and timing of dose administration (fractionation), and partly by the radiosensitivity of tissue stem cells within the radiation target volume. Knowledge of the radiation sensitivity of the stem cells concerned and accurate anatomical localisation of the treatment are essential to ensure that radiation affects only the tumour.

Recent progress in radiotherapy has derived from three background disciplines—biology, imaging, and radiation physics, especially as applied to linear accelerator technology. The biological basis of the effects of radiation is complex, and the wide range of radiation sensitivity seen in different types of tumour is intriguing.¹⁰ For example, with conventionally fractionated radiotherapy a dose of about 25 Gy is needed to control a 2 cm seminoma, a dose of 35-40 Gy to control a 2 cm lymphoma, and 60-65 Gy an epithelial tumour such as squamous cancer of the head and neck; doses over 70 Gy will not control a similarly sized high grade astrocytoma. Similar ranking of radiosensitivity is seen in the laboratory with cell lines derived from these human tumours.¹¹

Determining radiosensitivity

An important goal of current research is to determine the molecular mechanisms underlying differences

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in radiosensitivity. It seems that there may be differences in induction of damage to DNA, rejoining of DNA strand breaks, or repairing of damaged genes.¹² Analysis of cell lines from patients with ataxia telangiectasia, a recessively inherited syndrome characterised by extreme radiation sensitivity, has been informative.¹³ Scientists expect that the gene for the syndrome will be identified and cloned in the near future, which should help to identify at least one mechanism of radiosensitivity. Accurate prediction of individual tumour radiosensitivity is an important research avenue leading to more appropriate and more effective choice of treatment, radiation dose, and fractionation.¹⁴

At the cellular level it is clear that one mechanism of radiation resistance is rapid proliferation of tumour stem cells during protracted radiotherapy.^{15 16} Studies have shown that the potential doubling time of tumour cells is often as short as four days.¹⁷ During a seven week course of radiotherapy this could allow the number of tumour stem cells to increase by a factor of about 10 000. Cellular repopulation of a tumour may be even more efficient after the start of radiotherapy so it is desirable to give radiotherapy as rapidly as possible. Obviously, rapid treatment could be easily managed by giving a large dose of radiotherapy each day; however, this increases the risk of damage to healthy tissue. The solution to this problem has been to give several small doses of radiotherapy per day to shorten the overall treatment time, a strategy known as accelerated fractionation.

Several methods of accelerated fractionation exist, but one of the more extreme is continuous hyperfractionated accelerated radiotherapy (CHART). Pilot studies in non-small cell carcinoma of the bronchus¹⁸ and advanced head and neck cancers¹⁹ gave better results than were achieved in historical controls, and CHART is currently being studied in prospective national trials in Britain.

Improving sensitivity

A second target for improvement of radiotherapy has been based on the observation that tumour tissues have a poorly organised vascular supply and usually contain areas of hypoxic tissue.²⁰ Laboratory studies

show that hypoxia confers resistance to radiation and thus viable but hypoxic tumour cells may be a cause of treatment failure. Hyperbaric oxygen chambers have been used during radiotherapy to improve efficacy,²¹ and more recently drugs which mimic the effect of oxygen, such as misonidazole, have also been tried.²² These drugs were difficult to administer and of only slight benefit. One problem was that misonidazole produced neurotoxicity at high cumulative doses, but the second generation compound etanidazole, which has equivalent sensitising effects in hypoxic tissues, can be given in much higher doses before causing neuropathy²³; it is currently being investigated in prospective randomised trials in advanced head and neck cancers.

A more recent approach in the United Kingdom which has not yet been evaluated clinically is to use simple oxygen breathing together with nicotinamide, which is thought to improve the tumour's blood supply by inhibiting capillary shut down²⁴; animal models suggest that this considerably enhances the effects of radiation and clinical trials are planned.

Chemotherapy

The clinical effects of combining chemotherapy and radiotherapy have been generally disappointing.²⁵ It would be expected that these treatments, which act by different cellular mechanisms, would be at least additive in effect and, since their side effects tend to be distinct, that additive toxicity would be minimal. In practice the subject is immensely complex because of the variety of chemotherapeutic drugs and drug combinations that could be combined with radiotherapy and the number of different schedules of radiotherapy and chemotherapy, including neo-adjuvant chemotherapy, simultaneous chemotherapy, alternating chemotherapy and radiotherapy, or adjuvant chemotherapy after radiotherapy. There has proved to be a considerable risk of enhanced toxicity, especially when drugs and radiation are administered simultaneously.²⁶

Clinical experience so far has supported combined chemotherapy and radiotherapy only when each treatment attacks a different target. Examples include systematic control of acute lymphoblastic leukaemia with chemotherapy and irradiation of the chemotherapy sanctuary site within the cerebrospinal fluid space,²⁷ and early Hodgkin's disease, when a small radiation field is used to treat overt malignant lymphadenopathy and adjuvant chemotherapy to treat the possibility of widespread subclinical disease.²⁸

It has proved more difficult to establish a role for combining chemotherapy and radiotherapy to treat the same tumour mass. However, cancer of the anal canal, which is traditionally treated by radical excision and consequent bowel diversion, does seem to be just as successfully treated by relatively low doses of radiotherapy combined with simultaneous 5-fluorouracil and mitomycin C.²⁹ Even in this example it is as yet unclear whether similar results could be achieved with radiotherapy alone, and this is being compared in a trial by the United Kingdom Coordinating Committee for Cancer Research.

The use of chemotherapy before radiotherapy is thought to offer several advantages. These include a reduction in the amount of tumour to be treated, a reduction in the target volume or amount of normal tissue to be treated, a reduction in the degree of hypoxia in the primary tumour, and the early treatment of subclinical metastatic disease. This approach is currently being evaluated in advanced head and neck cancers, bladder cancer, and advanced cancers of the cervix among other sites.

Coronal magnetic resonance imaging showing ability of technique to localise the prostate and seminal vesicles precisely

New imaging techniques

The second major research pillar of radiotherapy is imaging. The development of computed tomographic scanning arguably had a more profound effect on radiotherapeutic practice than on any other specialty. It has greatly increased the accuracy of tumour staging in respect of the extent of the primary tumour, the presence of local nodal disease in sites relatively difficult to assess such as the mediastinum and abdomen, and the detection of small volume distant metastases. In addition computed tomography enables precise localisation of a tumour or organ within a two dimensional axial slice, the same axis on which radiation treatment plans are designed and calculated.³⁰ This offers a rapid and accurate computer based system for displaying the effects of alternative radiotherapy isodose plans, usually with combinations of two to four coplanar axial beams and compensating for differential beam attenuation in heterogeneous tissues or by irregular body surface contour.

Computerised planning is now complemented by the development of magnetic resonance imaging. The ability to image directly in the coronal or sagittal plane is of particular benefit and offers greater sensitivity in some sites such as the central nervous system. Sagittal imaging with magnetic resonance imaging has already proved invaluable in diagnosing spinal cord compression. It can be used to define precisely the vertical extent of tumour or normal tissues, thus providing the basis of the development of direct planning of radiotherapy on the magnetic resonance image.

It is now also possible to produce a three dimensional image by isotopic imaging. Positron emission tomography relies on the use of certain isotope tracers such as fluorine-18, oxygen-15, or iodine-124.⁶ The technique can provide both anatomical and functional assessments and has been used, for example, to define precise dosimetry of ¹²⁴I in treating iodine avid carcinomas of the thyroid, producing for the first time a rational basis for the dose of isotope and an explanation why certain metastatic sites respond less well to radiation.³¹

Linear accelerator

Developments in the technology of linear accelerator design also offer scope for advances in the precision of radiation treatment. One factor limiting the dose of radiation is the volume of normal tissue within the overall target volume.³² If the same tumour could be treated and normal tissue excluded then this could either reduce the risk of normal tissue damage or allow escalation of the radiation dose.³³

In the past radiation volumes have usually been cubes of tissue defined by the shape of the aperture of the head of the linear accelerator. The development of precise three dimensional imaging and of computer control of a range of treatment machine parameters now allows much more complex target volumes to be used.³⁴ A mechanism for producing these is based on a device called a multileaf collimator. The collimator shapes the edges of the radiation beam and in the past has been a single straight block. The replacement of this single block by a number of independent leaves offers the possibility of treating an irregular shaped tumour while excluding most of the normal tissue. Initial trials are currently quantifying the reduction in toxicity associated with "conformal radiotherapy," and if a reduction can be confirmed the next step will be to investigate dose escalations. Retrospective studies suggest that a dose escalation of 10% would for most tumours improve local control by 10-20%,³⁵ and the association between local control and survival³⁶ emphasises the potential of this technique for significantly improving survival from cancer over the next decade.

Box 3—Future developments in radiotherapy

Genetic diagnosis and characterisation
Management of premalignant lesions
Radiosensitising drugs
Isotope immunoconjugates
Conformal radiotherapy and three dimensional planning
Predictive testing of individual tumour and normal tissue radiosensitivity
Stem cell manipulation to protect normal tissues
Combined chemotherapy and radiotherapy
Altered radiation fractionation regimens using multiple treatments per day

Future of radiotherapy

Several factors have recently increased the importance of improving cancer therapies. Since cancer is mainly a disease of elderly people the rise in the age distribution of the population will certainly lead to an increased incidence of cancer in the community. At the same time, greater sophistication of surgery and radiotherapy and the development of effective chemotherapy regimens have increased the complexity of cancer treatments, improving prospects for effective palliation and cure. The rapid pace of research in both cancer biology and technology will ensure exciting advances in the use of radiotherapy in the coming decades (box 3).³⁷

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Letter from Poland

Post-totalitarian medicine

Karin Chopin

This is the last of three articles examining health issues in Poland

There is no way of knowing what democracy will end up looking like in Poland but here are some glimpses of it now.

Ania, a 45 year old obstetrician I met on my travels with the itinerant Polish deputy minister of health, Zbigniew Halat MD, invited me to her home to meet a group of people involved in various aspects of health care. Sitting round her kitchen table, they unfolded their lives for me.

Temptations of corruption

The young psychiatrist: "People have so much initiative in this country. This is our capital—but it must be exploited appropriately."

The head of a public health laboratory: "Our records aren't that good, I'll admit, but who are the World Bank, the World Health Organisation, or the Americans to come preaching to us? Rather a life in a Gdansk housing estate than a life in the Bronx. . . . And as for Sweden, people there are so bored that they all want to commit suicide."

The matron in charge of a nursing home: "We experienced the second world war and ever since, like most of the people in eastern Europe, I think we behave as if it never ended. Maybe this is why I am never really surprised that even 45 years afterwards there is still a lack of medicines, bandages, syringes. . . ."

"If the new laws permitting private clinics are not encouraged, one can safely predict that our citizens will continue to resort to the time honoured Polish custom of illegal payoffs—bribing doctors and nurses," the ward sister said. The corruption of the medical services in Poland is an undeniable social fact—"It's so much easier to bribe women doctors than men doctors," a friend from Warsaw once admitted. "How much more natural to give presents to a lady."

"We don't want to be like this," a young doctor protested, "but it is the system that forces us to. We are state employees, but the state is bankrupt and tells us to go and earn privately. You start out with noble intentions but then you find yourself having to succumb to the temptations of corruption just to survive." (Doctors currently earn 72% of the average national wage.) The newly appointed Polish minister of health, Dr Marian Miskiewicz, acknowledges that doctors accept bribes, especially in surgery, orthopaedics, and obstetrics, but he does not agree it is a common

practice. A Polish sociologist elaborated: "The trouble is that the health care system, basically designed in the early '50s, remains a highly centralised and rigid structure. The more rigid the structure and functions of a given institution, the more likely is a split between formal and informal structures."

The hospital manager: "Do you know that ambulances are called out four times more frequently in Poland than in the developed countries of western Europe?" (The minister of health had recently publicly deplored the disgracefully wasteful deployment of ambulances in Poland.) "A woman has a temperature and cannot be bothered to go down to the clinic, so she calls an ambulance. And then we don't have enough petrol to send out for the chap who's having a heart attack." Here I could not help interjecting: "But people in the West think of you also as a developed country." "What do you mean, 'developed'?" one of the company retorted in the fashionably self deprecating manner of the postcommunist era. "We're lagging at least 20 years behind you. Don't you realise that in the past decades our principal slogan was building communism, our main priority defence . . . an issue such as personal health was about number 193 on our list of national priorities."

I mention the young man I had seen on the way there, crouched in the doorway, covered with only a blanket to protect him from the falling snow. "I have AIDS, please help me," said his sign. "It is only a miracle that there are not more beggars, what with more than half of the working population living at the edge of poverty," explained Father Roman Indrzejczyk, pastor to the medical profession in Warsaw.

"And then, in the midst of all this, our anti-choice nationalist government is threatening our right to abortion and telling us to multiply, to given birth to more Poles!" Ania, our host, was enraged by officials in the Ministry of Health, who refuse to disseminate any birth control information, and accused them, the Chamber of Physicians, and the gynaecology establishment of being "criminals" for allowing abortions to proliferate by opposing birth control programmes. "They should be serving time," she said, "for the harm they're doing to women's health. And apart from anything else, abortion is a costly method if used as a primary resource of contraception as it is in Poland." She is involved in a passionate crusade to lower the

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