Introduction
Aims

Outline the importance of radiotherapy (RT), the evolution of technology and its impact on practice
Specific Learning Objectives

- Describe the value of radiotherapy in oncology
- Explain that RT is increasing in complexity
- Explain changes in RT technology in the context of advances in related disciplines
- Outline the potential consequences of changing technology
- Understand the problem of rising cancer incidence and challenges to cancer care.
A report by the Swedish Council on technology Assessment was published in 1996 describing the use of radiotherapy for cancers in Sweden in 1992. About 1/3 of cancer patients in 1992 received radiotherapy at some point during their illness. A second survey done in 2001 showed that the proportion of patients receiving radiotherapy had increased to 47%. This was similar to USA (49%), Australia (37% - 1998) and Canada (42% - 1995).
From the same study, the proportion of curative treatment for patients increased from 50% to 54% which is a relatively small increase. However the proportion of fields used for curative therapy increased more rapidly from 72% to 85%. This indicated an increase in utilisation of radiotherapy for curative therapy.
The proportion of patients treated with curative intent was similar in both county and regional hospital for many tumour sites. Some variation were seen for oesophagus (100% increase), lung (50%) and prostate (75%) cancers where a higher proportion were treated for cure in regional hospitals. Over 90% of gynaecological malignancies (except ovary) were treated with curative intent.
The dose fractionation regimes varied by tumour sites. The highest peak is mostly represented by breast cancer with median of 25 fraction treating to 50Gy (median). Rectal cancers had a low mean dose of 29 Gy in 8 fractions however most of these cancers were treated with 25Gy in 5 fractions regime represented by the small peak. Head & Neck (63.5 Gy/34 fractions) and prostate cancer (57 Gy/28 fractions) had the highest dose and most fractions.
Treatment for palliative intent has become shorter with fewer fractions. The graph shows the commonest regimes for palliation of bone metastases are 6-8 Gy in single fraction, 20-24 Gy in 4 or 5 fractions and 30 Gy in 10 fractions.
Radiotherapy in cancer treatment

Cost of radiotherapy

Curative treatment  € 6 050 (55 000 SEK)
Palliative treatment  € 1 870 (17 000 SEK)

6% of all cancer care cost

The cost of radiotherapy was about 6000 Euros for curative therapy and 1900 Euros for palliation. The total cost of radiotherapy (EBRT and brachytherapy) about 6% of total health care cost which compares favourably with the cost of chemotherapy which was about 12% of health care cost in Sweden in 1998.

Calculation on the cost of radiotherapy included

- Salary costs - based on numbers of employees and average salary + social overhead costs, etc
- Depreciation costs of equipment including purchase costs and 12 years of economic life and a 5% capital cost (12 years is chosen in order to make a comparison with the earlier report possible).
- Total cost of capital of building based on the stated cost of buildings per square metre upgraded by the consumer price index (CPI)
- Cost of services and overheads
The practice of oncology has changed due to the changes stated above. We shall review these changes in some detail.
Changes in oncology

- Science and technology
- Patient population
- Political, social and economic changes
Some of the main changes in oncology are due to advances in radiotherapy itself but many are also due to advances in imaging, in systemic therapies, surgery and also in translational research in oncology.
Advances in oncology

Technology

- Radiotherapy
- Imaging
- Systemic therapy
- Surgery
- Basic science and translation to oncology

We will talk about advances in radiotherapy first.
In the past, radiotherapy was mainly done as 2-dimensional (2D) planning. With technology, we are now able to plan and in 3D and also 4D.
Advances in radiotherapy technology

Hierarchy of modern RT technology

• 3D radiotherapy
  Conformal RT
  Stereotactic RT
  IMRT
    fixed field, dynamic
    arc (Rapidarc, VMAT, Tomotherapy)
  Proton therapy
  Image guided radiotherapy

• 4D radiotherapy
  Conformal RT (?)
  Adaptive RT

There are different forms of 3D and 4D radiotherapy with increasing complexity of the different treatment forms. 4D radiotherapy usually refers to gating of radiotherapy to compensate for organ movement e.g. lung and heart.
Further refinement in the process include the use of biological planning with PET and functional MRI which helps in delineating tumours which may be confused for normal structures or vice versa. The ability to fuse CT, MRI and PET images has been advantageous is certain tumour sites.
The main change from 2D to 3D radiotherapy has been in the planning. With image based planning ie CT and MRI scans, the anatomical structures of both normal tissues and tumours can be visualised during the planning process. The images shows normal tissue and tumour in the pelvis.
Further refinement in the process include the use of biological planning with PET and functional MRI which helps in delineating tumours which may be confused for normal structures or vice versa. The ability to fuse CT, MRI and PET images has been advantageous is certain tumour sites. The PET image shows the area of active tumour in the prostate which will not be apparent on a normal CT or MRI imaging. This also gives the potential advantage of focus treatment at the areas of highest tumour burden and highest risk of recurrence
In the past, radiotherapy has been given with simple rectangular fields. However, tumours and organs at risk (OAR) have variable shape and we need to avoid excess dose to OAR without missing tumours. Beam shaping then was limited to a greater extent with the use of standard blocks. Customised blocks were available but their use often limited by manufacturing time. With the advent of multi-leaf collimators (MLC), radiotherapy field can automatically be shaped to “conform” to the shape of the tumour in any particular treatment direction.
The use of MLC enable us to treat tumours according to their actual shape. However we were still delivering a uniform dose throughout the treatment field. As gross tumours have more clonogenic cells, these areas will need higher doses compared to areas of microscopic spread. By modulating or changing the intensity of radiation within a treatment fields, we are able to shape and sculpt the radiation dose even closer to the shape of the tumour and at the same time avoid excessive doses to OAR.
Improvement in beam modulation include the use of arc therapy which may be with tomotherapy with helical movement of a gantry, VMAT or RapidArc technology. With arc therapies, the number of “fields” is greatly increased and with beam modulation throughout the arc(s), the doses to normal structures are even out while maintaining dose conformity to the tumour.
Advances in radiotherapy technology

Conformal radiotherapy technology (3D & 4D)

- Planning
  - Anatomical/structural planning - CT and MRI
  - Biological planning (PET, functional MRI …)
  - Tumour, normal tissue function

- Delivery
  - Beam shaping alone
  - Beam modulation (IMRT incl. arc techniques)
  - Protons, heavy ions

- Quality assurance
  - including image guided RT

Proton beam therapy utilises the nucleus of hydrogen atom which has been stripped of it orbiting electron. As a form of particle therapy, protons deposit energy according to the Bragg’s curve with peak energy deposition at the end of its track (Bragg’s peak). With the sharp cut-off in energy deposition, a sharp dose gradient can be obtained between target volume and OAR. Heavy ion therapy has similar dosimetry advantages but with the added advantage of high LET radiation.
Improvement in imaging, planning and radiation delivery has to be coupled with quality assurance. One main issue with treatment delivery over several weeks is position and movement of the target volume between fractions ie interfraction movement. Portal imaging with films has now been replaced with electronic portal imaging devices (EPID). Improved method of imaging in delivery include the cone beam CT. These methods enable correction of patient position prior to therapy on a more regular basis.
Conceptually 4D radiotherapy utilises all the improvement and innovation in 3D radiotherapy. What 4D radiotherapy adds is the element of time and correction for intrafraction movement. This could be due to breathing and cardiac movement such as in lung cancer.
Central to all the improvement in radiotherapy is the patients who has not changed in the last 20 years. New technology and cutting edge treatment usually comes at a high cost in terms of capital expenditure and time.

**Advances in radiotherapy technology**

**Conformal radiotherapy technology (3D & 4D)**

- **Planning**
  - Anatomical/structural planning - CT and MRI
  - Biological planning (PET, functional MRI …)
  - Tumour, normal tissue
- **Delivery**
  - Beam shaping - cone
  - Beam modulation (IMRT incl. arc techniques)
  - Protons
- **Quality assurance**
  - Including image guided RT
One of this is improvement is patient immobilisation from using a standard thermoplastic mask to a relocatable frame immobilisation.
With conventional immobilisation, a 1cm margin around the clinical target volume is required to account for uncertainties especially patient movement in a less rigid immobilisation frame where maximal deviation may be up to 8mm.
With the rigid immobilisation frame using a bite block, a smaller 5mm margin is adequate as the average movement is less than 2mm.
In theory an even smaller 3mm margin may be adequate.
However smaller margins risk geographical miss and the difference in the brain volume spared between a 5 mm and 3 mm margin is small at the high dose areas 80-90% isodose.
Advances in oncology

Technology

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We will move to the other improvement relating to radiotherapy
Advances in imaging include multi-slice helical scanner, MRI with functional imaging, ultrasound for image guidance and PET-CT scan among others. These technical advances has improved detection of tumours and for radiotherapy planning, fusion of images from different sources (eg CT and MRI) allows more accurate tumour delineation.
Systemic therapies has improved in several aspects:
• Newer chemotherapeutic agents
• Improved supportive therapy eg anti-emetics
• Targeted therapies aimed at certain tumour characteristics such as mutated oncoproteins, and new targets such as tumour vasculature.

These new therapies have been integrated especially in advanced cancers where they help to prolong patients' lives with treatment. Previously many tumour sites eg renal and lung cancers have only 1 established line of palliative systemic therapy. It is common for patients to receive several successive lines of systemic therapies in these diseases. For example and EGFR mutated adenocarcinoma of the lung can receive EGFR targeted therapy like gefitinib or erlotinib as first line, then move to first and second line chemotherapy as appropriate.
Advances in oncology

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Surgery has advanced as well especially with minimally invasive surgery with reduced patient morbidity and usually similar outcomes. Improvement in anaesthesia and medicine allows more complicated surgeries to be performed e.g. sacrectomy.
Basic science research has benefited from improved computational power and along with it, the field of molecular medicine. It is now possible to do arrays of thousand of gene quickly to predict and prognosticate patients with different cancer.
Gene/molecular assay may allow us to move away from traditional models to predict prognosis. This example shows a gene array of 70 reporter genes which predicts for survival in patients with breast cancer as opposed to the St Gallen criteria. There has been many attempt to do similar work in literally all cancers. We now know that certain mutations in cancers are “driver” mutations and can be selectively targeted with drug eg EGFR and ALK in Non-small cell lung cancer
Advances in radiotherapy technology

What do we expect from new RT technology?

- Do things we can’t currently do
- Do things we can do but do them better
  - Operational efficiency
  - Clinical outcomes
Improvements in technology has enabled us to improved on certain aspects of radiotherapy. In the examples above, we can improve delineation of tumours and normal tissues, decrease margins around tumours, and improve accuracy of radiation delivery by looking at dosimetry as a volume. IMRT has allowed us to deliver radiotherapy in complex shapes such the chest wall.
With technology and automation eg computerised shape blocking with MLC, we can improve patient throughput, decreasing waiting time for patients. As we can see, in Sweden the proportion of patients for curative radiotherapy has increased with an increased in treatment fields. However with technology, the number of patient with could be treated in a single machine in a day has increased and therefore the cost of a radiotherapy fraction has remained similar from 1993 to 2001. Corrected for inflation, the cost of radiotherapy has actually become cheaper over time.
Advances in radiotherapy technology

What do we expect from new RT technology?

- Do things we can’t currently do
- Do things we can do but do them better
  - Operational efficiency
  - Clinical outcomes

Evaluating new technology

However these new technologies needs to be carefully evaluated in terms of patient outcomes.
Advances in radiotherapy technology

What do we expect from new RT technology?

• Do things we can’t currently do
• Do things we can do but do them better
  – Operational efficiency
  – Clinical outcomes

Evaluating new technology

reduce toxicity
improve tumour control

This could mean either improve tumour control with similar toxicity or reduced toxicity with similar patient outcomes ie improved therapeutic ratio.
Some of the disadvantages in new technology could be the use of complex treatment planning and delivery with marginal outcomes eg IMRT for palliation of bone metastases of lung cancer. This means increased utilisation of resources when simpler techniques are adequate with similar outcomes. An example is SBRT for multiple brain metastases where the survival of the patients are unchanged with the additional therapy.
Newer technologies will also require much more training and staff expertise to ensure safe delivery of treatment. Specialisation will be required with dedicated teams for the more complex treatment modalities eg IMRT, SBRT
With complex treatment such as IMRT, the treatment time is often prolonged and reduces patient throughput. Increased QA and machine accuracy results in increased maintenance and calibration times.
We have not fully evaluated the value and accuracy of incorporating new technologies such as PET-CT in planning. By reducing margins, we may underestimate microscopic tumour spread and results in reduced tumour control. Plan evaluation and planning are less intuitive and may result in increased toxicity. Increased data transfer and complex computer algorithms all increase the risk for errors in treatment delivery. Uncertainties in the computer algorithms also pose a challenge for early adaptors.

The Potential for Dose Dumping in Normal Tissues with IMRT for Pelvic and H&N Cancers
Presented in part at the 48th Annual Meeting of the American Association of Physicists in Medicine, July 30–August 3, 2006, Orlando, FL.
Nandanuri M.S. Reddy, Andrzej K. Mazur, Seshadri Sampath, Adrian Osian,
Brij M. Sood, Akkamma Ravi, Dattatreyudu Nori
Changes in oncology

- Science and technology
- Patient population
- Political, social and economic changes

We are now done with some aspects of science and technology
Changes in oncology

- Science and technology
- Patient population
- Political, social and economic changes

Let's move on to patient population.
Changes in oncology

- Science and technology
- Patient population
- Political, social and economic changes

Cancer epidemiology
Population age distribution
Predominant health problems/co-morbidity

There are 3 main issues in the changes in patient population namely 1, 2 & 3.
The rate of cancer rises with age. The graph indicates the increasing rate of breast cancer with age in the United States. The incidence is 1.5 per million at the ages 20-24 and is over 400 in women above 65 years, an increase of >25x. Therefore as the population ages, the risk for many cancers, not only breast cancer increases.
Along with the rise of cancer with age, the population pyramid in the world is changing especially in the developed countries. Reducing birth rate and increased life expectancy will move the population pyramid toward an elderly population. The graphs shows the expected changes in population pyramids in the Western Europe in the next 25 years. The average age of the population will increase and therefore the incidence of cancer will increase in tandem with the population age.
The graphs shows the expected changes in population pyramids in Japan in the next 50 years. The proportion of elderly population will exceed the younger population. This trend in population aging will be seen in many countries world wide and therefore the number of cancers in the world is also expected to increase.
The rising age in the general population will result in problems of rising incidence of cancer in an elderly population with issues of general frailty and multiple comorbidities especially diabetes and heart diseases. WHO project the incidence of cancer to rise and the number of death to increase by about 50% from about 8 million (2007) to 12 million (2030).
Changes in oncology

- Science and technology
- Patient population
- Political, social and economic changes
Political, social and economic issues varies with each country and within the country. This include priority and funding for cancer care and research. The incidence and mortality from cancers as a health problem do not necessarily translate into prioritisation and funding for care. For example pancreatic cancer is the 4th leading cause of mortality in the united states but receives less funding for research.
Summary

- The use of radiotherapy in cancer treatment has been increasing both in the palliative and curative settings.
- Coupled with improvement in medicine, technological improvement in radiotherapy has made treatment planning and delivery more accurate.
- More complex radiotherapy pose certain advantages and disadvantages.
- Cancer incidence world wide is increasing and the role of radiotherapy will increase in tandem with it.
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