Principles of radiotherapy and radio-chemotherapy of malignant tumours

Polgár Cs.\textsuperscript{1,2} –
National Institute of Oncology\textsuperscript{1},
Chair of Oncology,
Semmelweis University\textsuperscript{2}
Multidisciplinary treatment of malignant tumours

- Surgery (S)
- Radiotherapy (RT)
- Systemic therapy
  - Chemo-, hormone-, immuno-therapy + targeted therapies

- Combined (multidisciplinary) management:
  - S + RT
  - S + concomittant radio-chemotherapy (RCT)
  - Primary RCT
  - Preop. RT + S
• **Radiotherapy**: Clinical modality dealing with the use of ionizing radiation in the treatment of patients with malignant tumours.

• **Aim**: To deliver precisely measured dose of irradiation to a defined tumour volume with as minimal damage as possible to the surrounding healthy tissues, resulting eradication of the tumour.

• (selective killing of malignant cells)

• **Teletherapy** = external beam irradiation (EBI)

• **Brachytherapy (BT)** = irradiation with sealed radioactive sources placed close to or in contact with the tumour.
Role of RT in the management of tumours

- New cancer cases/year in Hungary: 80,000 → 2030 ≈ 100,000 new cases

- In 45-55% of cancer patients RT is mandatory!
- In 20-25% of RT patients a 2^{nd}. course of RT (reirradiation) is needed.

- Dominating therapy leading to cure or long-term survival:
  - Surgery – 49%
  - Radiotherapy – 40%
  - Systemic therapies – 11%

Annual number of RT patients in Hungary

<table>
<thead>
<tr>
<th></th>
<th>1993</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<tbody>
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<td>RT patients#</td>
<td>12,685</td>
<td>31,097</td>
<td>32,194</td>
<td>33,162</td>
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</table>
Intention of radiation therapy

• Intention to treat:
  – Curative (total dose: 50-80 Gy)
  – Palliative (total dose: 20-60 Gy)

• Preoperative RT (down-staging & down-sizeing, devitalisation of tumour cells before surgery or organ preservation surgery)

• Postoperative RT (eradication of microscopic residual tumour cells)

• Definitive or primary RT

• RT alone

• Combined RCT (head & neck, cervical, bladder, anal canal, rectal, lung)

• Combined radio-biotherapy (head & neck: cetuximab + RT)
Preoperative RT

- Rectal ca.
  - T1-2 N0 - preop. RT
  - T3-4 N1-2 – preop. RCT

- Esophageal ca.
  - preop. RCT

- Cervical and endometrial cancers
  - preop. brachytherapy
Postoperative RT

- **Prostate ca.**
  - T3-4, N1

- **Breast ca.**
  - After breast-conserving surgery (All pts.)
  - After mastectomy (T3-4, ill. N+)

- **Gastric ca.**
  - Postop. RCT

- **Head & Neck cancers**
  - Postop. RT
  - Postop. RCT (R1 resection, >1 pos. LNs)

- **Brain tumours**
  - Glioblastoma – Postop. RCT

- **GYN cancers**
  - Endometrial ca. (postop. RT: G3, pT1b, N+)
  - Cervical ca. (postop. RCT: R1 resection, pos. LNs, infiltr. parametria)
  - Vulvar ca.
Primary (Definitive) RT/RCT

- **Anal canal cc.**: Curative RCT

- **Prostate ca.**
  - Low risk: Brachytherapy (BT) OR external beam irradiation (EBI) alone
  - EBI + BT boost

- **GYN cancers**
  - Endometrial ca. – RT alone (EBI + BT)
  - Cervical ca.
    - St. I/A-I/B1: RT alone (EBI + BT)
    - St. I/B2, II/A-B, III/A-B, IV/A: concomittant RCT + BT
  - Vaginal ca.: RT or RCT

- **Head & Neck tumours**
  - T1-2 N0 – RT alone
  - T3-4 N1-2 – RCT

- **Lung ca.**: Curative RT or RCT

- **Bladder ca. (muscle invasive; ≥T2)**: TUR + curative RCT
Palliative RT

• Cerebral metastases – Whole brain irradiation (WBI)
  – Stereotactic radio-surgery (SRS)

• Spinal compression

• Bone metastases (pain and/or danger of fracture)

• Vena Cava Superior (VCS) syndrome (decompression)

• Palliative brachytherapy
  – GYN cancers – stop bleeding
  – Lung and esophageal tumours – avoid obstruction
Cutaneous lymphoma – Primary RT

Before RT

After RT
Squamous cell ca. of the nose – Primary RT

Before RT

After RT
Dosimetric principles

- Only the energy of ionizing radiation absorbed by the tissues has biological effect!
- The absorbed energy is quantified with the term "absorbed dose"

**Absorbed dose**: absorbed energy by a unit of tissue mass.
- SI unit: Gray (Gy)

\[ 1 \text{ Gy} = 1 \text{ J/kg} \quad 1 \text{ Gy} = 100 \text{ cGy} \]

**Dose rate**: absorbed dose by time unit.
- SI unit: Gy/min, Gy/h
Modifying factors of the biological effects of RT

- Radiation quality (photons, electrons, protons)
- Energy
- Total dose
- Fracionation
- Radiosensitivity of tumours and normal tissues
- Irradiated volume
- Radiosensitizers (hyperbaric O₂, RCT, hypertermia)
- Radioprotective drugs (e.g. Salagen – protection of salivary glands)
Teletherapy equipments

- **Kilovoltage equipments:**
  - X-ray therapy machines: 40-300 KV Roentgen-photons

- **Megavoltage equipments:**
  - Telecobalt unit: 1.25 MV gamma-photons
  - LINear ACcelerators (LINAC): 4-29 MV photons OR electrons
Definition of target volumes for radiotherapy treatment planning

GTV = Gross Tumor Volume  CT, MRI, US
CTV = Clinical Target Volume
PTV = Planning Target Volume

macroscopic tumor volume
microscopic tumor spread
safety margin
Informations needed for radiotherapy treatment planning

- Data on tissue density – for dose calculation (CT)
- Anatomic information (CT, MRI, US)
- Biological information (PET)
- 4D information (3D + change in time)
Treatment planning

- Reproducible patient positioning + CT-based treatment planning

- 3D-CRT: use of individual, irregular fields conforming to the 3 dimensional shape of the target volume - “multi-leaf collimator”

Termoplastic mask fixation
3D-CRT = individual, irregular fields conforming to the 3D shape of the target volume

Intensity modulated RT (IMRT) = modulation of intensity within the radiation field
Intensity modulated radiotherapy (IMRT)

- Step-and-shoot IMRT
- Dynamic IMRT
  - Sliding window
  - IMAT (arc therapy)

Intensity profile builds up as the sum of individual radiation field segments.
Intensity modulated radiotherapy (IMRT)
Image-guided radiotherapy = IGRT

**Goal:** to avoid inaccuracies caused by daily set-up error, change of patient anatomy, and internal organ motions

**Head & Neck tumour:**
Change of patient anatomy during the course of RT:
- tumour shrinkage
- loss of weight
IGRT using LINAC + integrated CT on-rail

Pretreatment CT

CT

LINAC
IGRT using LINAC + integrated CT on-rail

RT delivery with 180° table rotation
IGRT using megavoltage cone-beam CT (MV-CBCT)
IGRT using kilovoltage cone-beam CT (kV-CBCT)
Stereotactic radiosurgery (SRS)

- Single-fraction high-dose irradiation for limited volume neurological malformations
- Fixation and 3D localization with stereotactic head-frame
- High-precision CT/MRI-based 3D imaging and treatment planning
- Rotating irradiation (arc therapy) using small and highly focused beams

Dose prescription: 16 Gy to the 50% isodose
Stereotactic Ablative Body RadioTherapy = SABRT

Technical needs:

- 4D-CT
- 6-degree of freedom treatment coach
- kV-CBCT
Stereotactic Ablative Body RadioTherapy = SABRT
Irradiation of moving targets – Conventional technique

Breathing cycle

Wide radiation safety margin
Irradiation of moving targets – Gated radiotherapy

Narrow safety margin ->
Less side-effect
and/or
Dose escalation

Narrow radiation safety margin
Cyberknife = Robotic arm + LINAC

2 diagnostic X-ray tubes

Two perpendicular flat-panel silicium detectors
Helical tomotherapy – CT + LINAC

TomoTherapy is the first system to integrate CT Imaging and Intensity Modulated Radiation Therapy into the same treatment machine.
Rationale for adding chemotherapy to radiation

Seiwert TY et al. (2007) The concurrent chemoradiation paradigm—general principles

*Nat Clin Pract Oncol* 4: 86–100
Interactions of RT and CT

- **Additive:** The overall effect of RT + CT = the sum of the separate effect of each modality.

- **Subadditive:** The overall effect of RT + CT < the sum of the separate effects of the two modalities.

- **Synergistic:** The overall effect of RT + CT > the sum of the separate effects of the two modalities.

- **Antagonistic:** The overall effect of RT + CT < the effect of RT alone radioprotective effect.
Possible interactions of RT and CT in tumours and normal tissues

<table>
<thead>
<tr>
<th></th>
<th>Tumour</th>
<th>Normal tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>sinergistic</td>
<td>antagonistic</td>
</tr>
<tr>
<td><strong>Reality</strong></td>
<td>additive</td>
<td>subadditive</td>
</tr>
</tbody>
</table>
### Evidence based indications of RCT according to disease entities

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Indication and treatment</th>
<th>Commonly used agents</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper aerodigestive tract cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>Locally advanced HNC—primary or adjuvant treatment</td>
<td>Cisplatin, 5-FU, FHX, cetuximab</td>
<td>Improved organ preservation and survival compared with radiation alone</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>Stage IIIb, nonoperable nonmetastatic disease</td>
<td>Cisplatin, carboplatin/paclitaxel, cisplatin/etoposide</td>
<td>Curative approach in poor surgical candidates or IIIb disease</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>Limited stage disease</td>
<td>Cisplatin/etoposide</td>
<td>Curative in ~20% of patients</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Locally advanced disease</td>
<td>Cisplatin, 5-FU</td>
<td>Survival benefit, increased cure rates, organ preservation</td>
</tr>
<tr>
<td>Gastrointestinal malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Neoadjuvant</td>
<td>5-FU</td>
<td>Improved sphincter preservation, decrease in local and distal failures</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>Mainstay of curative treatment</td>
<td>5-FU, MMC</td>
<td>Improved organ preservation</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Adjuvant</td>
<td>Cisplatin, 5-FU</td>
<td>Some data indicate a survival benefit</td>
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<tr>
<td>Pancreatic cancer</td>
<td>Adjuvant, unresectable locoregionally advanced tumors</td>
<td>5-FU</td>
<td>Improved locoregional control, possibly a survival benefit</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Adjuvant, unresectable locoregionally advanced tumors</td>
<td>5-FU</td>
<td>Some data indicate a survival benefit</td>
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<tr>
<td>Gynecological and genitourinary cancers</td>
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<td></td>
<td></td>
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<tr>
<td>Cervical cancer</td>
<td>Primary modality</td>
<td>Cisplatin, 5-FU, hydroxyurea</td>
<td>Improved local and distal control, organ preservation</td>
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<tr>
<td>Bladder cancer</td>
<td>Primary modality</td>
<td>Cisplatin</td>
<td>Improved local control</td>
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<tr>
<td>Other cancers</td>
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<tr>
<td>Glioblastoma</td>
<td>Adjuvant</td>
<td>Temozolomide</td>
<td>Survival benefit</td>
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<tr>
<td>Sarcoma</td>
<td>Neoadjuvant</td>
<td>Doxorubicin</td>
<td>Downstaging, improved organ preservation</td>
</tr>
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Clinical forms of brachytherapy (BT) I

- interstitial BT (prostate, breast, oral cavity, base of tongue)
- intracavitary BT (GYN, nasopharyngeal cc.)
- intraluminal BT (lung, esophagus)
- superficial ”moulage” BT (skin, hard palate, tonsillar fossa)
Clinical forms of BT II

- **Low-dose-rate:** 0-2 Gy/h
- **Medium-dose-rate:** 2-12 Gy/h
- **High-dose rate:** > 12 Gy/h
- **Pulsed-dose-rate:** ultra-fractionated HDR
- **After-loading technique:**
  - remote after-loading of the radiation source
Standard BT applicators for the treatment of cervical cancer
Intracavitatary + interstitial CT/MR compatible applicators
Role of RCT followed by brachytherapy boost

Before RCT

Chemoradiation

HDR-BT boost

Kirisits et al. – AKH Wien
CT-based brachytherapy of cervical cancer

Intracavitary + interstitial BT
Interstitial brachytherapy of vulvar cc.
CT-based interstitial breast brachytherapy

Preimplant CT

Postimplant CT
US-based prostate HDR brachytherapy
US-based permanent implantation prostate brachytherapy (PIPB)
Carcinoma of the floor of mouth – CT-based interstitial BT
Base of tongue tumour – CT-based interstitial BT
Intraluminal lung + esophageal brachytherapy
Radiotherapy centers in Hungary (n=12)

Regional comprehensive cancer centers (n=5):
NIO, Univ. Pécs, Univ. Szeged, Univ. Debrecen, Szombathely
Number of pts. treated with RT in Hungary (n=33.116)

<table>
<thead>
<tr>
<th>Location</th>
<th>1993</th>
<th>2012</th>
<th>2013</th>
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<tr>
<td>Budapest – OOI</td>
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Thanks for your kind attention!