Principles of radiotherapy and radio-chemotherapy of malignant tumours

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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: $76,000 \Rightarrow 2030 \approx 100,000$ new cases
- In $60\%$ of cancer patients RT is mandatory!
- In $20-25\%$ of RT patients a 2\textsuperscript{nd}. course of RT (reirradiation) is needed.

Annual number of RT patients in Hungary

<table>
<thead>
<tr>
<th>Year</th>
<th>RT patients#</th>
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<tbody>
<tr>
<td>1993</td>
<td>12,685</td>
</tr>
<tr>
<td>2012</td>
<td>31,097</td>
</tr>
<tr>
<td>2013</td>
<td>32,194</td>
</tr>
<tr>
<td>2014</td>
<td>33,162</td>
</tr>
<tr>
<td>2015</td>
<td>28,359</td>
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<tr>
<td>2016</td>
<td>33,376</td>
</tr>
<tr>
<td>2017</td>
<td>33,024</td>
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</table>

+ 20,339
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 → 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
• 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
Ca. of the lip – 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 \textit{"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-photon

- **Megavoltage equipments:**
  - Telecobalt unit: 1.25 MV gamma-photon
  - LINear ACcelerators (LINAC): 4-29 MV photons OR electrons
LINAC + CT “on rail”

LINAC + kV cone-beam CT

LINear ACcelerator = LINAC

Gantry

CT

Multi-leaf collimator = MLC

3D conformal radiotherapy = 3D-CRT

CB-CT

Flat-panel detector
Definition of target volumes for radiotherapy treatment planning

GTV = Gross Tumor Volume  
CTV = Clinical Target Volume  
PTV = Planning Target Volume

**macroscopic tumor volume**

**microscopic tumor spread**

**safety margin**

CT, MRI, US
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"
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

Ideal intensity profile

Achievable intensity profile using MLC
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
IGRT using LINAC + integrated CT on-rail

RT delivery with 180° table rotation
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

kV-CBCT

6D-treatment coach
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

Two perpendicular flat-panel silicium detectors

2 diagnostic X-ray tubes
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><strong>Upper aerodigestive tract cancers</strong></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><strong>Gastrointestinal malignancies</strong></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>
</tr>
<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>
</tr>
<tr>
<td><strong>Gynecological and genitourinary cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Primary modality</td>
<td>Cisplatin, 5-FU, hydroxyurea</td>
<td>Improved local and distal control, organ preservation</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Primary modality</td>
<td>Cisplatin</td>
<td>Improved local control</td>
</tr>
<tr>
<td><strong>Other cancers</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glioblastoma</td>
<td>Adjuvant</td>
<td>Temozolomide</td>
<td>Survival benefit</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Neoadjuvant</td>
<td>Doxorubicin</td>
<td>Downstaging, improved organ preservation</td>
</tr>
</tbody>
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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
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
Intraluminal lung + esophageal brachytherapy

3 weeks
Before BT
After BT
Thanks for your kind attention!