INTRODUCTION TO RADIATON ONCOLOGY

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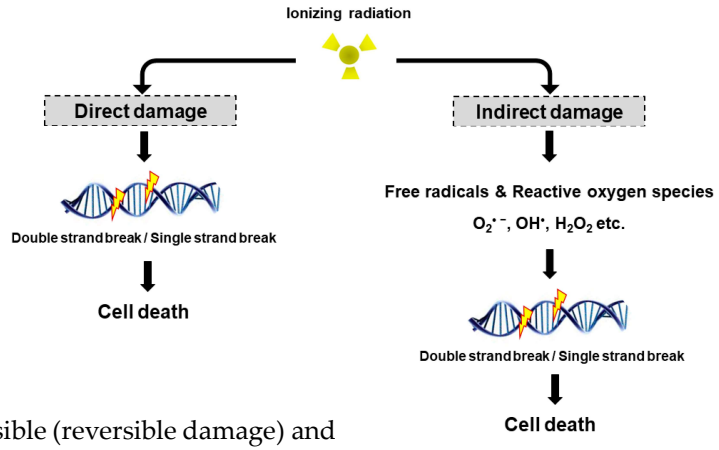
Radiotherapy

- The treatment of disease with ionizing radiation.
- Included in oncology multidisciplinary treatment approach – radiation oncology
- Treatment of malignant diseases and certain benign conditions (vascular disorders, degenerative diseases...)
- Local/Locoregional treatment method
- *Abscopal effect*
- More than 50% of all oncology patient undergo radiotherapy during treatment.

Interaction of Ionizing Radiation with Matter

The radiation effects - through a series of physical and chemical reactions:

- In the physical stage - ionization and excitation of atoms of living matter molecules.
- Chemical stage - by direct and indirect action of ionizing radiation
  - Direct action (target theory): the target can be a cell, or any of its structures (DNA, RNA, enzyme).
  - In interaction with radiation, structures can be reversibly or irreversibly damaged.
  - Indirect action (free radical theory): effect on extracellular and intracellular fluid, formation of free radicals (dominant mechanism of action on biological systems)
- Biological stage – inactivation of any subcellular structures
  - DNA damaged and to what extent?
  - Repair mechanisms/cell death
  - Damage can be lethal (irreversible damage), sub-lethal, when recovery of the damaged cell is possible (reversible damage) and potentially lethal damage.



Hur W. Et al. Int J of Mol Sci. 2017.

5R - factors influencing the response of tumor and normal tissue to ionizing radiation

- **Repair** - after each RT, interaction of radiation with cellular structures and repair of damage occurs within a few hours. Cells of different tissue – different dynamics of the repair process, depending on the proliferative potential.
- **Repopulation** - approximately the same percentage of vital tumor cells and healthy tissue is eliminated during radiation with each fraction. The loss of cells stimulates the surviving cells to divide more intensively. The final effect of repopulation is a tumor mass increase before each new fraction, but also the recovery of damaged healthy cells.
- **Redistribution** - tumor cells and healthy tissue show the highest radioresistance in the S and G1 phase of the cell cycle, while they are most sensitive in the M (mitosis) and late G2 phase, where there is a difference in radiosensitivity between tumor cells and healthy tissue.
- Irradiation of cells that are in different phases of the cell cycle results in the devitalization of those in the radiosensitive phase - immediately after irradiation cycle, the largest number of surviving cells are in the radioresistant phase.
- **Reoxygenation** - increased oxygen concentration increases, and decreased concentration decreases the radiosensitivity of cells. With their growth, solid tumors often exceed the capacity of the existing vascularization, so zones of hypoxia and necrosis appear in the tumor tissue.
- By applying fractionated radiation regimens during the interfraction interval, reoxygenation of previously hypoxic cells is achieved, thereby increasing their radiosensitivity.

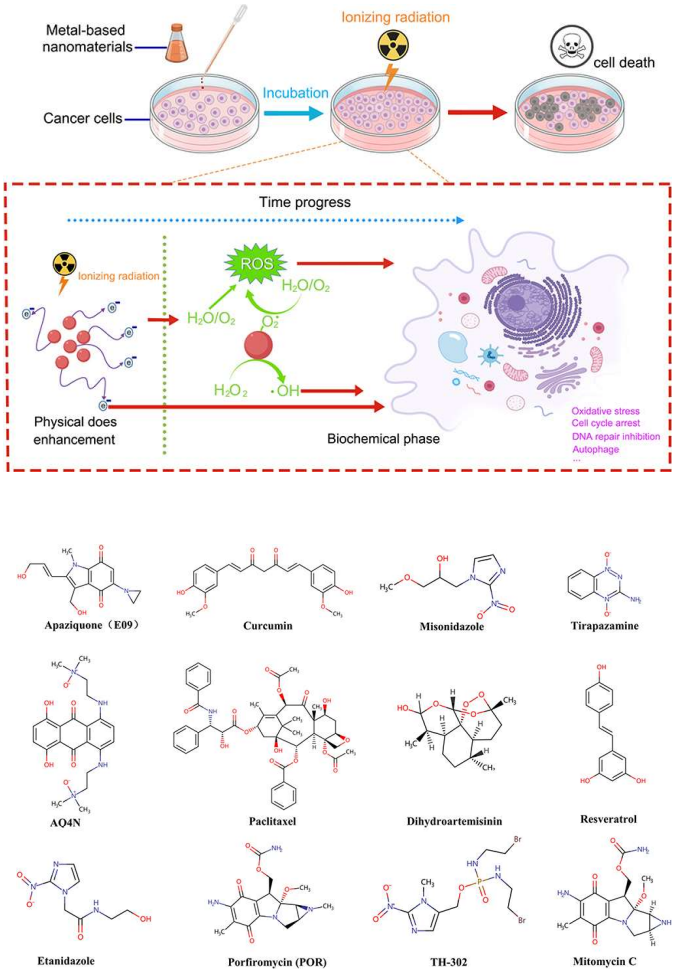
Radiosensitivity

- Malignant tumor cells are dedifferentiated and have increased mitotic activity, which makes them more radiosensitive compared to the cells of healthy tissues from which they arise (*Bergonié-Tribondeau* law).
- The greater the difference in radiosensitivity between the cells of normal tissues and the tumor, the greater the possibility of treating the tumor with radiotherapy.

- **Radiosensitive** tumors: lymphomas, leukosis, germinal tumors (seminoma, disgerminoma), nephroblastoma, Wilms' tumor, Ewing's sarcoma;
- **Moderately radiosensitive** tumors: tumors of the head and neck region (cancers of the skin, lips, paranasal cavities, epipharynx, oropharynx, hypopharynx, larynx), GI tumors (cancer of the esophagus, anus, rectum), gynecological tumors (cancer of the cervix, endometrium, vulva , vagina), urological tumors (prostate cancer, bladder cancer, non-seminoma testicular tumors), lung, breast, thyroid gland and brain tumors
- **Radioresistant** tumors: bone and soft tissue tumors (osteosarcoma, chondrosarcoma, fibrosarcoma, synoviosarcoma, liposarcoma, angiosarcoma, etc.), kidney adenocarcinoma, GI adenocarcinomas (stomach, pancreas, liver, bile ducts) and melanoma.

Radiosensitisers

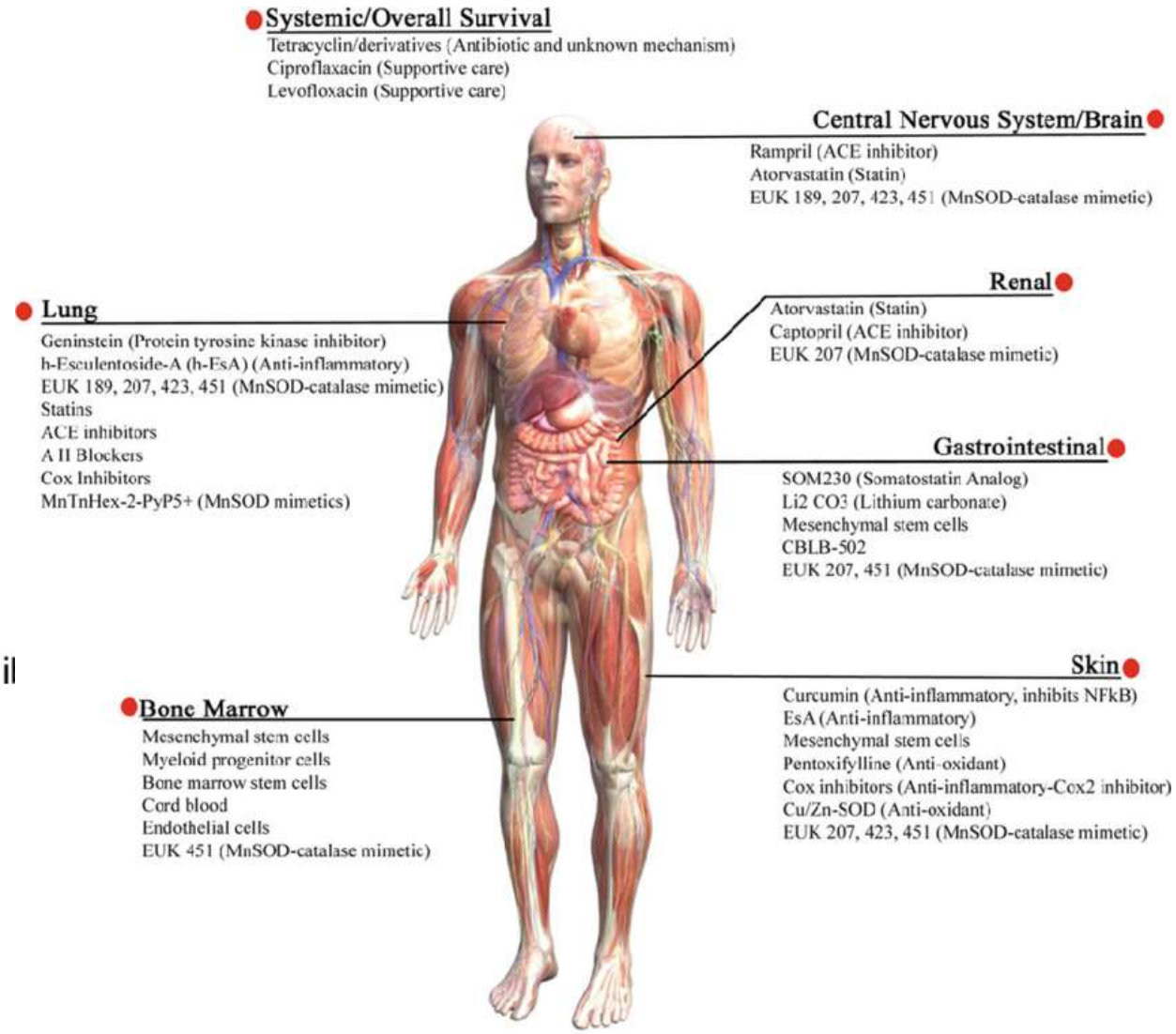
Hyperbaric oxygen
Carbogen
Nicotinamide
Metronidazole and its analogs (misonidzole, etanidazole, nimorazole)
Hypoxic cell cytotoxic agents (Mitomycin-C, Tirapazamine)
Membrane active agents (procaine, lidocaine, chlorpromazine)
Radiosensitizing nucleosides (5-Fluorouracil, Fluorodeoxyuridine, Bromodeoxyuridine, Iododeoxyuridine, Hydroxyurea, Gemcitabine, Fludarabine)
Texaphyrins (motexafin gadolinium)
Supressors of sulfhydral groups (N- Ethylmalemide, Diamide and Diethylmaleate)
Hyperthermia
Novel radiosensitizers (paclitaxel, docetaxel, irinotecan)



Gong L. Int J of Nanomedicine. 2021.

Radioprotectors
Radiation mitigators

Palifermin
Halofuginone
TGF-ß
Keratinocyte growth factor
ACE inhibitors (Captopril, Enalapril, ramipril)
COX-2 inhibitors/NSAIDS (celecoxib, aspirin, il



- Coleman S. N. ALERT. 2014.

DOSE FRACTIONATION IN RADIATION ONCOLOGY

- The total dose of radiation applied in one fraction or divided with a time gap in between does not give the same radiobiological effect.
- If the total dose is applied in one fraction or a smaller number of fractions, the radiation effect on the biological system is greater than if the same dose is applied in a larger number of fractions – TDF (Time Dose Fracction) or EQD2 (biologically equivalent doses).
- The longer the irradiation time, the higher the total dose required to achieve a radiobiological effect.

Fractionation regimes

- Standard (conventional) fractionated radiation – previously the most frequently applied radiation regimen in daily clinical practice. Therapeutic dose 1.8 to 2 Gy per day.
- Hyperfractionated radiation - radiation fractions are applied, with a minimum time interval of 4 to 6 hours in one day. The aim is to improve local control, expected higher acute adverse events.
- Hypofractionated radiation - application of the total tumor dose in a smaller number of fractions, whereby a dose of 3 to 6 Gy, or greater per fraction is applied.
- Single radiation fraction - applying therapeutic dose in one fraction (SRS, IORT, palliative single shoot).
- Continuous radiation - in brachytherapy, with Low Dose Rate (LDR).

Radiotherapy treatment aim can be:

- Radical - in order to achieve a complete and permanent remission of the disease (the application of a radical dose of radiation is often limited by the radiotolerance of healthy tissue)
- Prophylactic (elective) - by irradiating a region that is not clinically affected, but the subclinical presence of malignant cells is possible
- Palliative - in order to control symptoms and improve the quality of life (pain reduction, prevention of bleeding, compression symptoms)
- Preoperative - goal: downstaging, downsizing. Precedes surgical treatment, intent - reduction of biological potential.
- Postoperative (adjuvant) - eradication of possibly remaining malignant cells in order to reduce the local relapse rate (LRR). Clearly defined indications by localization.
- Intraoperative radiotherapy (IORT) - direct irradiation of the tumor bed during the surgical procedure.
- Chemoradiotherapy (CRT) - to improve treatment results, can be a concomitant therapeutic regimen - simultaneous application or in a sequential therapeutic regimen - applying chemotherapy after completed radiotherapy, or vice versa. Synergism of two methods. More frequent treatment complications.

Radiotherapy treatment can be perform as:

- Brachytherapy (direct or close contact with the radiation source)
- External beam radiotherapy (EBRT) (distance beetwen patient and radiation source – ''source-skin distance, SSD'').