Conclusion: RT remains an important modality in the treatment of NHL.

SP-0640
Reducing late radiation effects by devising better treatments for lymphoma patients
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Background: Cure rates of patients with lymphoma have improved significantly over the last decades because of improved diagnostics, chemotherapy and radiotherapy. There is, however, a large variety of late effects following treatment for lymphoma including decreased fertility, hormonal disturbances, pulmonary toxicity, soft tissue damage, second malignancies and cardiovascular diseases leading to considerable morbidity and excess mortality. The long-term burden of lymphoma treatment is determined by a combination of all late effects. Since (non) Hodgkin lymphoma (NHL) frequently occurs at relatively young ages, survivors are subject to the full spectrum of early and late side effects of therapy. Over time knowledge and awareness of late effects following cancer treatment have increased and treatment policies have been adapted accordingly.

Improvement of treatment: Several randomized clinical trials have been performed to determine the role of radiation in lymphoma patients especially in HL patients. Radiation indication, target volume and dose have been subject of study. Since many important long-term complications (like second malignancies and cardiovascular toxicity) are related to radiation dose and volume, reduction of these treatment parameters are expected to ameliorate long-term toxicity (1,2).

Reducing volume
Over the last decades radiation volumes in lymphoma patients have changed considerably because of better knowledge in the spread of the disease through improved diagnostic possibilities and improved systemic treatments.

In HL patients for instance radiation field-sizes have been reduced from subtotal-nodal or extended field to involved field or, more recently, involved site or involved node leading to smaller volumes of normal tissues exposed to significantly lower radiation doses. A word of caution, however: involved node radiotherapy should not be applied strictly when optimal pre-chemotherapy imaging is not available to the radiation oncologist. In this situation more generous margins should be used including the whole “site” where the lymphoma was located before chemotherapy.

Furthermore, in early stage gastric lymphoma patients, total abdominal irradiation has been replaced by radiotherapy limited to the stomach and the surrounding lymph nodes using modern radiation techniques in selected patients only.

Reducing dose
For both HL and many subtypes of NHL systemic treatment options have improved significantly. These improvements have led to the possibility to reduce both radiation dose and volume while maintaining similar treatment outcomes (3). In the past generally doses up to 40-45 Gy in fractions of 2 Gy were used. Nowadays radiation doses in curative setting usually vary from 20 to 30 Gy and sometimes 36 Gy in fractions of 2 Gy.

Technical improvements
Deep inspiration breath hold
In selected patients with mediastinal disease the use of deep inspiration breath hold and intensity modulated radiation therapy is expected to decrease exposure of the coronary arteries, heart, and lungs especially when the target volume is located in the upper part of the mediastinum (4).

Proton therapy
Another emerging technology is proton therapy. Proton therapy is associated with a substantial reduction in radiation dose to critical organs, such as the heart and lungs, and therefore has the potential to improve not only the therapeutic ratio, but also both event-free and overall survival.

Conclusions
Patient tailored radiotherapy in lymphoma patients using lower doses, smaller and better-defined radiation volumes than in the past, based on modern imaging and using conformal radiotherapy are expected to lead to an improved therapeutic ratio and decreased late effects. Further improvements are expected with the introduction of even more modern radiation techniques like deep inspirational breath hold.

Selected references

SP-0641
Targeting the use of lactate by tumor and endothelial cells in combination or not with radiotherapy
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Hypoxia is a cancer hallmark impacting tumor progression and treatment. From a biological standpoint, it promotes (i) a glycolytic switch formally corresponding to uncoupling glycolysis from oxidative phosphorylation and accelerating the glycolytic flux in order to fulfill the energetic and biosynthetic needs of cancer cells, (ii) an angiogenic switch, and (iii) a metastatic switch. From a therapeutic standpoint, hypoxia provides radiosresistance notably because oxygen is molecularly involved in the stabilization of radiation-induced DNA damage. Among several interventions intended to improve oxygen availability to radiosensitize tumors, mathematical models indicate that those targeting tumor cell metabolism would be particularly efficient. Indeed, even a moderate inhibition of tumour cell respiration is predicted to significantly increase tumor oxygenation.

Switching to a glycolytic metabolism is associated with the abundant release of lactate, the level of which positively correlates with tumor aggressiveness in patients. Although it was often considered as a mere glycolytic end-product, our work over the last 5 years showed that lactate is a direct tumor growth-promoting factor influencing tumor metabolism and angiogenesis. We first evidenced that lactate is a metabolic substrate promoting glucose to fuel the oxidative activities of oxidized tumor cells. This metabolic preference supports a metabolic symbiosis in which (i) hypoxic/glycolytic tumor cells produce lactate, (ii) oxygenated/oxidative tumor cells consume lactate sparing glucose, and (iii), consequently, glucose is made optimally available to fuel accelerated glycolysis in the hypoxic tumor cell compartment. Tumor-associated fibroblasts may constitute an additional source of lactate. We next found that lactate is also a signaling agent promoting tumor angiogenesis. Lactate oxidation to pyruvate, the LDH reaction, is shared by both metabolic and signaling pathways. However, although pyruvate can be consumed in the mitochondrion to sustain oxidative ATP production, it can also competitively inhibit HIF-1 prolyl hydroxylases even under normoxia. Lactate thereby activates the transcription factors HIF-1 in oxygenated tumor and endothelial cells and NF-κB in endothelial cells, thus triggering pro-angiogenic VEGF, bFGF and IL-8 signaling.

We finally found that the metabolic and signaling use of lactate requires monocarboxylate transporter 1 (MCT1), a passive lactate-proton symporter located at the outer membrane of oxygenated tumor and endothelial cells where it facilitates lactate uptake. Targeting MCT1 pharmacologically or with RNA interference first induced a glycolytic switch and, therefore, oxygen sparing in the oxygenated tumor cell compartment. It consequently eradicated the hypoxic tumor cell compartment by virtue of glucose starvation, whereas the remaining MCT1-positive tumor cells could be efficiently treated with X-ray radiotherapy as they were fully reoxygenated. MCT1 inhibition also blocked lactate signaling and tumor angiogenesis.

Conclusively, our study shows (i) that lactate is a pleiotropic tumor growth-promoting factor, and (ii) that MCT1 inhibitors combine antimitabolic, radiosensitizing, and anti-angiogenic tumor effects within a same molecule. A first MCT1 inhibitor, AZD-3965, is currently entering into clinical trials in UK.

SP-0642
Extracellular matrix: What is it good for? Absolutely everything
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Tumors similar to normal tissues contain extracellular matrix (ECM). Through integrin cell surface receptor binding, cells are integrated into multicellular structures and eventually tissues and organs. Different from normal tissues are the amount and organization of ECM in cancers giving rise to tumor angiogenesis, pressure, tumor cell invasion, cancer stem cell niche development, and therapy resistance. Our understanding of adhesion-mediated tumor cell radio- and chemoresistance are still in its infancy. Evidently, integrin signaling activates key pro-survival determinants such as focal adhesion kinase, Akt, MAPK among many others, while the structural integrin-mediated cell-actin connection controls cell morphology including nuclear matrix and chromatin organization. Studies in normal cells such as fibroblasts or endothelial cells have revealed that all known cell functions ranging from cell survival to metabolism are co-regulated by...
integrins. Particularly for tumor cells its remains critical that therapy resistance emerges from mutually and cooperatively interactions between integrins and transmembrane growth factor receptors. How exactly such interactions are executed and what consequences result from them for tumor cell behavior and bypass signaling for therapy resistance will be the great challenge to understand in the next years. Additional impact on these processes arises from extracellular matrix stiffness in tumors, which is commonly observed relative to normal tissues. Despite the fact that ECM stiffness essentially contributes to tumor progression, it remains unclear what its role is for tumor cell resistance to standard radio(chemo)therapy. What our current view on the above mentioned aspects of tumor biology and therapy resistance is will be presented.

**SP-0643**

**Tumor radiosensitization by autophagy-inhibition**

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Hypoxia is a common feature of tumors and an important contributor to malignancy and treatment resistance. We and others have shown that a lysosomal degradation pathway, autophagy, which enables cells to recycle and redirect nutrients to adapt to metabolic stresses, is required for the survival of hypoxic cells. Consequently, autophagy inhibition sensitized tumors to irradiation as determined by tumor growth delay experiments. Our research focuses on unraveling the molecular mechanisms that are required for the activation of autophagy during hypoxia and to exploit these for therapeutic purposes. During this presentation, I will describe some of our recent findings and how we think that we can use autophagy targeting to improve tumor treatment. For example, we identified a radiosensitive subset of glioblastoma that, when use autophagy targeting to improve tumor treatment. For example, we identified a radioresistant subset of glioblastoma that, when metabolically challenged, is highly dependent on autophagy for survival. Its dependency on autophagy provides a novel opportunity to delay recurrence of the tumors after treatment.

**SP-0644**

**Hypoxia promotes EMT and stemness through suppression of Dicer**

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Tumor hypoxia is associated with aggressive disease and poor clinical outcome in many types of cancer. This is due in large part to the ability of hypoxia to influence important signalling pathways that augment metabolism, angiogenesis, genetic instability, and metastasis. Recent data suggests that hypoxia may also promote stemness in normal stem cell microenvironments, and in the oxygen deprived microenvironments of some solid tumors. We have discovered a novel potential mechanism that may underlie these observations. We found that hypoxia causes a rapid loss of the enzyme DICER, an essential component in the miRNA biogenesis pathway. This occurs through an epigenetic mechanism that results in transcriptional silencing of the DICER1 gene. Loss of DICER during hypoxia or following genetic knockdown results in a defect in the creation of mature and functional miRNA, and a corresponding increase in miRNA precursor forms. However, loss of DICER has a differential effect on individual miRNAs and resulted in a particular loss of members of the miR200 family. Loss of miR200 during hypoxia or following DICER1 knockdown results in derepression of its target ZEB1 and induces an epithelial-mesenchymal transition (EMT) characterized by an altered cell morphology, loss of E-cadherin, and acquisition of N-cadherin and vimentin. In human mammary epithelial cells transformed with dominant oncogenes, exposure to hypoxia or knockdown of DICER1 induces EMT and acquisition of stem cell properties including increased sphere formation, and expression of the cell surface markers CD24<sup>−</sup>,CD44<sup>+</sup> which have been shown to enrich in tumor initiating cells. Importantly, both EMT and acquisition of stem cell properties are prevented during hypoxia by overexpression of miR200b. DICER1 and hypoxia were also found to be negatively correlated in a large clinical series of breast cancer gene expression studies and both low DICER expression and high hypoxia were associated with poor outcome. Collectively, these data indicate that hypoxic suppression of DICER leads to increased stemness through repression of the miR200 family and suggest this effect may contribute to the known association of hypoxia with metastasis and poor outcome in patients.

**SP-0645**

**Medical physics for the future: How to get ready?**

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There is no doubt that the story of Medical Physics has been a story of incredible success. Academic and professional contributions that Medical Physics has made in the areas of radiation therapy and imaging are too many to list. The academic advances have been successfully translated to the clinics, leading to wide recognition of Medical Physics as an essential health profession. This success has lead to maturation of the field, reflected in strong consolidation of the professional part of Medical Physics. Particularly in the US, this consolidation has been accelerated with the recently implemented strict CAMPEP (Commission on Accreditation of Medical Physics Educational Programs) requirements that have tightened education and training requirements for Medical Physics professionals, leaving little room for academic freedom and expansion of the field. This consolidation exposed challenges in front of the academic part of Medical Physics. Concerned about the long-term future of Medical Physics as an academic and professional discipline, the American Association of Physicists in Medicine (AAPM) has established a Working Group on the Future of Medical Physics Research and Academic Training (WG FUTURE) with a charge “to initiate, coordinate and lead activities to secure sustainable growth and improvement in the long-term future environment for high quality research and academic training of physicists in medicine.”. WG FUTURE has already had a significant impact through development of the AAPM Research Strategic Plan, organization of a series of “Expanding Horizons” workshops and initiation of many other activities.

In this talk, the activities of WG FUTURE will be outlined, particularly activities of high interest to the ESTRO members. In addition, potential synergistic activities will be proposed to further strengthen global collaboration of medical physicists and secure long-term future of the field.

**SP-0647**

**How does medical physics retain responsibility for the patient?**

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In the question how the physicist retains responsibility for the patient, is related to the legal as well as ethical considerations. In this paper we will provide an overview of the legal implications in different countries of the ESTRO membership as well as the US. On an ethical level there is a need to decide to what level the physicist carries responsibility. It is clear however that the physicist is definitely responsible in providing the tools to the physician and to make sure these tools provide the advertised accuracy and quality control for these tools needs to be available. On the other hand when the patient is being treated it is still the physicians’ responsibility to decide which treatment (if any) will be most beneficial to the patient.

The question then remains: “which is the physicists’ responsibility?” By using specific examples from errors and use cases we will investigate the different possibilities. Finally, a town hall round of questions is started to start discussions.

**SP-0648**

**Future developments of medical physics inside and outside radiotherapy**

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Abstract not received