contains one intruterine and two vaginal catheters. The presence of an RTT during the vaginal impression is essential as support to the radiation oncologist. Based on the tumour topography representation, the RTT is asked to manufacture a personalized mould adapted to the patient anatomy. The catheters positions are placed according to the physician’s recommendations.

Before each treatment, the RTT performs quality controls on the afterloader. These controls, made under physicist responsibility, include all the standard verification of the correct dwell position and agreement between air kerma rate calculated by the afterloader at the date of treatment for the source and the one measured at the date of calibration.

In the operating room, the RTT checks the patient’s identity and is in charge of the patient installation. She prepares the medico-surgical instrumentation table and assists the radiation oncologist during the procedure. At the end of the implantation, she fills the technical documentation and gives it to nurses. Once the implantation is performed, the patient is transferred to the MRI scanner. With the help of a physician, the RTT inserts MRI compatible dummy sources into the catheters allowing a visualization of the intrauterine and vaginal positions of the sources. The delineation and the dosimetry are realised on MRI images. This optimized 3D dosimetry, the RTT takes part in every step of the treatment. She creates the patient file in the treatment planning system (TPS), imports, checks the MRI images, and reconsists the case. During the treatment, the RTT is in charge of the treatment workflow; she records all the treatment parameters on a register and informs the patient on her treatment before it starts.

In conclusion we have shown that the RTT is involved in every step of the patient’s RT treatment. Her role is crucial in the treatment workflow and needs specific skills to be accomplished. In addition to versatility, the RTT needs a rigor, thoroughness, empathy and patience.

SYMPOSIUM: LYMPHOMA: TO IRRADIATE OR NOT TO IRRADIATE

SP-0638
Role of RT in Hodgkin lymphoma in the PET-era (with a link to the EORTC H10 study which has been recently closed)
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The question is whether PET response-adapted strategies can be devised to deliver radiation treatments to a selected group of patients. The background of this persistent and sometimes emotional quest is complex but can be summarized as follows: first, combined modality treatments are superior to chemotherapy alone in terms of overall and progression-free survival, as demonstrated by a recent meta-analysis (1). Second, chemotherapy is very efficacious. Third, radiation treatments be get late complications such as second tumors and cardiovascular diseases. Fourth, the late effects of ABVD might have been grossly underestimated (2). PET response-adapted strategies can be implemented if PET predictive values are highly significant and reliable. Preliminary conclusions can be obtained from a small number of non randomized studies after completion of planned treatments. The negative predictive value (NPV) for the intermediary and end of treatment PET assessments was excellent (> 95%). In contrast, the positive predictive value (PPV) was extremely low (15%-20%) and therefore systematic biopsies are always highly recommended to confirm the diagnosis. As, in all likelihood, the role of radiation therapy in advanced Hodgkin lymphoma will remain extremely reduced, we will focus on ongoing trials in early-stage Hodgkin lymphoma. Currently, there are 4 randomized trials and one non-randomized study. The relatively small Vancouver non-randomized study suggested that radiotherapy could be avoided in approximately 80% of the patients with a negative PET after 2 ABVD cycles. Among the randomized trials, the randomized trials with a favorable response to RT are the Vancouver non-randomized trials and the randomized trials in early stage Hodgkin lymphoma patients entered in 2 of them (mostly IA and IIa: GHSG and the UK Rapid trial). In two others (EORTC-LYSA-FIL H10, Euronet-PHL-C1), all early stages were included. The preliminary results of the UK Rapid trial suggest that radiotherapy was not necessary in patients with a negative PET scan after 2 to 3 cycles of ABVD (75% of the patients). On the other hand, an interim analysis of the much larger H10 trial demonstrated that PET-negative patients after 2ABVD cycles had a significantly higher risk of local recurrence or progression. The experimental arm with PET-negative patients was prematurely closed for further accrual. The very preliminary results of the ongoing Euronet trial, suggest that radiation treatments were not performed in a substantial number of PET-negative patients (only 40% of the French patients received radiation therapy: 26%, 41%, and 50% in the TG1, TG2, and TG3 groups respectively).

Conclusions. Very preliminary results seem to suggest that an early PET response might provide a reliable basis for individualized response-adapted treatment strategies. However, the final results of the ongoing randomized trials should be awaited before drawing definite conclusions that may be applicable in clinical practice. Moreover, it must be emphasized that difficulties remain: the still predominant positron emission tomography (PET) assessment and the absence of a clear understanding of the underlying biological mechanisms of PET avidity.

Role of radiotherapy in the treatment of non Hodgkin lymphoma in the Rituximab era
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Radiotherapy (RT) is the most effective single modality for local control of non Hodgkin lymphoma (NHL), and it is an important component of the treatment of many patients. The previously applied wide field and involved field techniques are no longer recommended and have been replaced by defined volumes based on modern imaging and the ICRU concepts, the so-called involved site RT. Moreover, there is increasing evidence that the RT doses used in the past are higher than necessary. The goal of modern smaller field radiotherapy is to reduce both treatment volume and treatment dose whilst maintaining efficacy and minimising acute and late sequelae.

B-cell lymphomas constitute 85-90 % of lymphomas in adults. The large majority expresses CD20 antigen. The development of anti-CD20 antibodies, first Rituximab approved in 1997, significantly improved treatment results when added to standard chemotherapy for patients with advanced disease. The question is now if the role of RT in B-cell lymphomas has changed.

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma. For stage I-II patients without bulk or elevated LDH, standard treatment based on somewhat conflicting randomized trials was brief chemotherapy (3 cycles of CHOP) followed by IFRT. No randomized trial is available using R-CHOP, but retrospective analyses indicate that RT improves outcome also in this setting. For patients with risk factors 3 cycles of R-CHOP may not be enough. A positive PET-scan after R-CHOP has a low predictive value, and most PET+ cases achieve complete remission (CR) after RT. For advanced disease earlier studies showed benefit from RT in patients achieving a CR in some studies but not in others, whereas patients achieving only partial remission (PR) benefit from RT to residual masses. However, recent randomized studies in patients treated with Rituximab indicate that RT to initial bulk or extranodal disease, even in CR patients, improves outcome. Randomized evidence indicates that 30 Gy is a sufficient dose, at least in CR patients.

Follicular lymphoma (FL), grade 1-2 is the most common indolent lymphoma. In early stage disease RT is still the only proven way for potential cure. Standard treatment is RT alone, and randomized evidence indicates that 24 Gy is a sufficient dose. Unfortunately, this treatment seems to be underused. For patients with advanced disease if treatment is indicated, Rituximab with or without chemotherapy is given, but has not been shown to be curative. Low dose (2 Gy x 2) RT is an effective palliative treatment for locally symptomatic disease.

Marginal zone lymphomas are indolent B-cell lymphomas, most often extranodal and localized. RT (24-30 Gy) is curative in the majority of localized cases, and is the preferred treatment (except for H. pylori positive gastric). Rituximab may be used if RT is contraindicated. Advanced disease is uncommon, nocurative treatment exists, treated like FL.

Mantle cell lymphomas are B-cell lymphomas with an aggressive behaviour. Very rarely these lymphomas are localized, and RT may be curative. No curative systemic treatment exists, and although Rituximab improves response rate and time to treatment failure it has little impact on survival. Advanced disease is incurable, but local palliative RT can be very effective.

Primary cutaneous B-cell lymphomas are treated with local RT if solitary or regional. Only the aggressive type, DLBCL leg type, is also treated systematically (R-CHOP) for patients who can tolerate it. Patients with generalized disease are treated palliatively with Rituximab containing regimens, and local RT is given for palliation of symptoms.

T-cell lymphomas are CD20 negative, and treatment is not influenced by the introduction of Rituximab. Most T-cell lymphomas present as advanced disease. RT has no role in the treatment except for palliation, and in cases of large cell cases. In NK/T-cell lymphomas, cutaneous anaplastic large cell lymphomas, and mycosis fungoides, where RT is an important part of treatment.
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, chemoradiotherapy 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 radiotherapy 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

SYMPOSIUM: MICROENVIRONMENT

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 radioresistance 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 tumor 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 produced by glucose to fuel the oxidative activities of oxygenated 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 prolylhydroxylases 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 antitumor, 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 multicompartments and eventually tissues and organs. Different from normal tissues are the amount and organization of ECM in tumors giving rise to increased intratumoral 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...