SP-0387
Does this house believe that we can avoid surgery in responder rectal cancer patients? For the motion
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Pathological complete response (pCR) after chemoradiation therapy (CRT) is increasingly reported with a range between 10% and 30%. Patients with pCR have been reported to have a favorable oncological outcome (LR 1.2% CSS 95.6%) and it rises the doubt that major surgery with total mesorectal excision (TME) is probably an overtreatment. This is specially true regarding the high rate of short and long-term morbidity (evacuative, urinary and sexual dysfunction) associated with it. The question is how to pre-operatively predict pCR with an high level of accuracy. Clinical complete response (cCR) is not homogeneously defined and is not fully reliable in predicting pCR (25-85%). Full-Thickness Local Excision (FTLE) after CRT in major responders to neoadjuvant treatment should be regarded not as a cancer treatment but as the best diagnostic tool to confirm pCR. The accuracy of FTLE in the definition of (T) it is ≈ 99% and in ypT0, looking at reported series it is possible to predict the absence of lymph node involvement with an accuracy of ≈ 96%. Clinical trials to confirm validity of a less invasive therapeutic approach are required.

SP-0388
Against the motion
H. Rutten
Catharina Ziekenhuis, Eindhoven, The Netherlands

Abstract not received

SYMPOSIUM: THE IMPACT OF OMES AND OMICS, ON RADIATION ONCOLOGY

SP-0389
The future selection of patients for radiotherapy clinical trials - will molecular signatures & biomarkers help?
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Abstract not received

SP-0390
Radiotherapy and targeted drugs: which and how many pathways to target?
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Recent insights into the molecular mechanisms underlying tumor cell radiosensitivity have led to the identification of a large number of potential targets for rational intervention. Blockade of EGFR signaling, interference with new blood vessel formation, and inhibition of DNA damage repair, are a few examples of attractive strategies to increase tumor response in combination with radiation (and/or chemotherapy). However, despite many studies on radiation-targeted drug combinations, the clinical benefit of these new strategies has been small so far. It is therefore essential to consider which possible mechanisms underlie this limited success. A series of studies demonstrated that multiple factors will have to be considered and point to opportunities to optimize the combination radiation-targeted agents.

Focusing on a single target or signaling pathway may be an effective strategy for a specific tumor, but not for others. For example, targeted inhibition of the BRAF(V600E) oncoprotein is highly effective in the treatment of melanoma, but not of BRAF(V600E) mutant colon tumors. RNAi genetic screening revealed that blockade of EGFR signaling shows strong synergy with BRAF(V600E) inhibition. Mechanistically, BRAF(V600E) inhibition causes a rapid feedback activation of EGFR, explaining continued proliferation in the presence of BRAF(V600E) inhibition. Similarly, a feedback mechanism has been described in EGFR-driven cancers in which MEK inhibition leads to activation of PI3K/akt signaling. Thus, targeting multiple pathways may be required to obtain sufficient radiosensitizing conditions.

Normal tissue toxicity limits the therapeutic ratio of any anti-cancer therapy, including radiation-targeted drug combinations. A recent randomized phase II study at the NKI evaluating cisplatin-based chemoradiation with or without cetuximab in locally advanced NSCLC demonstrated no survival advantage, but was associated with significantly more grade ≥ 3 acute toxicity.

Scheduling between radiation and targeted agents represents another important mechanistic aspect to take into account. This is of particular relevance for anti-angiogenic drugs. There are both preclinical and clinical data that demonstrate that treating tumors with this class of targeted agents is associated with a time window of opportunity, characterized by vessel normalization and a decrease in intervascular distance. Treatment with tyrosine kinase inhibitors is associated with improved oxygenation and perfusion, which may differ among tumors, radiation (and chemotherapy) will exert their optimal anti-tumor effect.

Hence the right target with a biologically optimal dose discriminated radiosensitization from single agent cytotoxicity. Whereas dose escalation studies frequently aim at identifying the maximum tolerated dose, radiosensitizing strategies require doses of targeted agents (for chemotherapy) to sufficiently modulate the predefined target. These doses are not necessarily associated with single agents dose-limiting toxicity. PARP inhibitors such as olaparib may be effective as radiosensitizers at significantly lower doses than required to exert single agent activity. It is therefore important to establish sensitive biomarkers that assess PARP inhibition in the context of radiosensitization efficacy. Such biomarkers for radio-sensitization efficacy of PARP inhibitors are currently evaluated in a phase I-II dose-escalation study in locally advanced NSCLC combining olaparib with standard chemoradiation at the NKI.

In summary, radiation-targeted agent combinations are attractive but challenging strategies that require a rational approach and careful study design.

SP-0391
Radiation and targeted therapeutics: Omics-Omics-Optimization (Pathways-Procedures-Patients)
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Modern radiation oncology will require a new synergy between high-precision radiotherapy protocols and innovative approaches for biological optimization. From a clinical perspective, new insight into molecular radiobiology will provide a unique opportunity for rational patient stratification based on actionable tumor targets, enabling the parallel design of next-generation trials that formally examine the effect of adding targeted therapeutics to radiation, together with the critically important assessment of radiation dose-volume relationships of both tumor response and normal tissue toxicity. In considering the use of systemic agents with presumed radiosensitizing activity, this will need particular attention in defining patient eligibility. The presentation will highlight principles in addressing clinical evaluation of combined-modality targeted therapeutics and radiotherapy.

Objective: On review of 90 recent early-phase trials combining targeted therapeutics and radiation, a number of actionable tumor signaling pathways involved in tumor proliferation, angiogenesis, and hypoxia were found to have been examined, with tolerability, safety, and efficacy as study endpoints. In these trials, treatment outcome was diverse, ranging from tolerable to significant toxicities, and from lack of additional via significant responses to unexpected early disease progression. Our review did not specifically investigate whether the systemic agents had been evaluated with respect to biological mechanisms of radiosensitization in appropriate preclinical tumor models prior to the specific clinical studies.

Omic - Procedures for identifying relevant actionable targets: In medical oncology early-phase studies of systemic targeted therapeutics, the prevailing gold-standard for patient selection is based primarily on the detection of tumor gene aberrations. In contrast, in radiotherapy, the composite activities of a range of signaling effector proteins determining tumor resistance to radiation may conceptually comprise a functional biomarker of actionable targets for radiosensitization. Hence, thersinostic profiling technologies should ideally reflect all interacting signaling pathways involved in tumor proliferation, angiogenesis, and hypoxia. Using array technology with tyrosine kinase substrates, we have shown that composite tumor signaling mediated by high phosphatidylinositol-3-kinase activity may be a biomarker for treatment stratification in rectal cancer patients undergoing neoadjuvant chemoradiotherapy. Optimization - Patient eligibility: Treatment protocols should maximize the specific detriment of interruption in radiation delivery and the consequent negative impact on the probability of tumor control. Hence, only patients that are not candidates for curative radiotherapy protocols should be regarded as eligible in a trial setting of integrating tolerability and efficacy in the context of combined radiation with a targeted therapeutic. Of note, in our investigation of recent early-phase combined-modality trials, one-third of studies with
curative (definitive or preoperative) therapeutic intent reported significant toxicity. To enable full interpretation of outcome toxicity data, both the specific tumor type and the related disease site being irradiated will require both to be specified as study eligibility criteria, together with a description of detailed radiation dose-volume dependencies within the treatment protocol. This will also facilitate identification of adverse radiation effects that are separate from toxic effects of the systemic agent. In addition to determining treatment safety, proof of biological activity and – ideally – target-dependent radiosensitizing ability of the investigational agent should be regarded as a study objective. Finally, if the study eligibility criteria employ the principles of defining both the tumor type and anatomic location of the specific target volume being treated, the resultant homogeneous patient population will also ultimately enable treatment response evaluation.

SYMPOTOM: INACCURACIES AND NEAR MISSES IN RADIOTHERAPY AND HOW TO ADDRESS THEM

SP-0392

Taxonomies for synoptic reporting and analysis of radiation treatment incidents
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Synoptic reporting and analysis of incidents in radiotherapy, and elsewhere in medicine, means being directed to providing key descriptive information in a structured format. There are three principal advantages of synoptic reporting: completeness, lack of ambiguity and searchability. Firstly, the reporting and analysis forms, if well designed, will ensure that all key information required to understand the incident and to develop corrective actions is recorded. This meets the requirement of completeness. The problem of ambiguity can, to some extent, be mitigated by restricting responses to key elements of the report and analysis to predetermined lists of options with carefully thought out language. The third benefit of structured synoptic reporting is that the databases into which reports and analyses are entered can be rapidly searched and hence major issues flagged and trends identified. Additional flexibility is included in an incident learning system through incorporating free text boxes where the reporter and analyst can augment the basic information entered.

The presentation will commence with an overview of a generic incident learning system and will then introduce SAFRON and the U.S. national incident reporting initiative as examples of the implementation of such systems. The structure of these will be discussed identifying the synoptic and free text components. To understand where in the radiotherapy process the incident originated and where it was discovered process maps are used. The severity of an incident, which often determines the priority of the response and corrective actions, is an important component of the synopsis although severity can be hard to establish particularly as the consequences of a clinical RT incident may not be apparent for weeks or months. In order to implement effective corrective actions it is important that they follow from the identification of basic causes/contributing factors. The approaches of SAFRON and the U.S. implementation will be discussed in the context of these three synoptic elements.

As well as enhancing the quality and safety of radiotherapy, properly constructed incident learning systems can also help us to identify the most effective impediments to error propagation. Both SAFRON and the US system specifically include safety barriers in the synoptic reporting structure. The reporter/analyst is invited to identify those barriers which the error penetrated and that barrier at which the error was stopped.

Synoptic reporting aids clear communication and analysis of radiotherapy incidents. It can also guide the development of an efficient safety program by discriminating between more effective and less effective safety barriers.

SP-0393

The patient experience as a catalyst for change
M. Murphy 1

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Following the death of her son as a result of medical error, the focus of Margaret’s work relates to seeing adverse events as having the potential to be catalysts for change as well as being opportunities for learning, identifying areas for improvement and preventing recurrence.