observed that KB1P tumors were initially hypersensitive to fractionated local delivery of radiotherapy, but could not be eradicated: tumors relapsed and eventually acquired stable resistance. To investigate whether HR was restored in the resistant tumors, we studied 53BP1 and RAD51 irradiation-induced foci formation. Surprisingly, while restoration of HR was prominently found in tumors that acquired resistance to PARP or topoisomerase I inhibition, we did not find it in radiotherapy resistant tumors. To investigate this discrepancy more closely, 53BP1 and related repair factors were knocked out in cell lines derived from the KB1P model using the CRISPR/Cas9 technology. Consistent with our in vivo data, clonogenic assays showed that the knock-out of 53BP1 conferred strong resistance to PARP1 inhibition. Intriguingly, the lack of 53BP1 sensitized BRCA1-deficient cells to radiotherapy. An in vitro competition assay confirmed the selection to maintain a functional 53BP1 allele during radiotherapy treatment. Based on the KB1P model, we therefore hypothesize that resistance mechanisms that frequently occur in response to PARP1 inhibition sensitize cells to radiotherapy. These results, and their significance to human cells, are currently further validated in additional in vivo models including patient-derived tumors.

References

Teaching Lecture: SBRT/SABR for oligometastatic disease

SP-0386
SBRT/SABR for oligometastatic disease
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Introduction: Stereotactic ( ablative) body radiotherapy (SBRT/SABR) has been successfully used in the treatment of metastatic lesions and could be considered as a "curative option" for some oligometastatic patients. Multiple studies have described significant local control in brain, lung and liver metastases of various primary cancers. Results suggest SBRT/SABR could be an effective treatment extending patients' life span.

Study: For example in our retrospective study involved 90 patients, designed to test potential effectiveness of SBRT in the treatment of oligometastases irrespective of primary. Between July 2007 and June 2010, 90 patients were treated with robotic SBRT/SABR for hepatic or pulmonary metastatic lesions. A total of 113 liver and 26 lung metastatic lesions in 52 men (58%) and 38 women (42%) were treated. Median follow-up was 17 months. Median age at treatment was 65 years (range, 23-84 years). Primary cancers were 63 GI, three lung, eight breast, four melanoma, three neuro-endocrine tumors, and three sarcomas. Median diameter of the lesions was 28 mm (range, 7-110 mm) for liver and 12.5 mm (range, 5-63.5 mm) for lung. Local control rates at 1 and 2 years were 84.5% and 66.1%, respectively. Two-year overall survival rate was 70% (95% CI: 55-81%).

Conclusion: SBRT/SABR treatment is well tolerated with low toxicity rates. It could represent an interesting treatment option for oligometastatic patients not amenable to surgery, even when patients had been pre-treated with chemotherapy. The biological models behind the observed clinical efficacy are currently scrutinized. New combined treatment may be driven from such promising results.

Teaching Lecture: Advanced treatment strategies for head and neck cancer

SP-0387
Advanced treatment strategies for head and neck cancer
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Optimal treatment of head and neck squamous cell carcinoma (HNSCC) patients requires well organized interdisciplinary coordination. Standard treatment of locally advanced HNSCC is chemoradiation or surgery followed by chemoradiation. Cisplatin containing chemotherapy remains standard of care in combination with concurrent radiotherapy. Neither neoadjuvant chemotherapy, nor treatments with targeted drugs have changed this standard, although some data suggest that cetuximab can be used as substitute for cisplatin especially in HPV/p16 positive disease. Combinations of cetuximab or other EGFR1 antagonists with chemoradiation did not improve patient's outcome, but added toxicity. Overall, attempts to improve clinical outcome in locally advanced HNSCC with targeted drugs and new cytostatic drugs have not been successful. The situation is different in locoregionally recurrent HNSCC not amenable for local treatment and in metastatic disease. In these patients, the addition of cetuximab to cisplatin and 5FU resulted in a significant survival benefit and consequently is considered as standard of care.

HPV/p16 positive HNSCC represents a distinct entity, which is more sensitive to radiotherapy and cytotoxic drugs. Several studies testing deescalated treatments are being tested in randomized trials. However, deescalated is not yet recommended outside clinical trials.

Neoadjuvant chemotherapy followed by radiotherapy +/- chemotherapy or cetuximab, and primary chemoradiation have been shown to allow for organ preservation especially in laryngeal cancer in the majority of patients without compromising overall survival. However, adequate selection of patients is critical to obtain organ preservation with good functional outcome.

Recent technological developments in surgery and radiotherapy like transoral robotic surgery and radiotherapy using intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image guided radiotherapy (IGRT), and stereotactic body radiation therapy (SBRT) have been evaluated in cohort studies and a few randomized trials. These technologies are suitable for decreasing early and late toxicity and improvement of functional outcome, but have not been shown to improve locoregional control, disease free survival, and overall survival. The available data on the topics addressed above will be shown and discussed.