radiotherapy patients. Simple radiation protection models should be used only with extreme care for risk estimates in radiotherapy, since they are developed exclusively for low dose. When applied to scatter radiation, such models can predict only a fraction of observed second malignancies. Better semi-empirical models include the effect of dose fractionation and represent the dose-response relationships more accurately. The involved uncertainties are still huge for most organs and tissues. A major reason for this is that the underlying processes of the induction of carcinoma and sarcoma are not well known. Most uncertainties are related to the time patterns of cancer induction, the population specific dependencies and to the organ specific cancer induction rates. For radiotherapy, treatment plan optimization these factors are irrelevant, as a treatment plan comparison is performed for a patient of specific age, sex, etc. If a treatment plan is compared relative to another one only the shape of the dose-response curve (the so called risk-equivalent dose) is of importance and errors can be minimized. One of the largest remaining uncertainties is the precision of the dose distribution which is the basic input into all risk-estimate-models. Dose calculation and/or measurement are as precise as approximately 5% in the treated volume of the patient. However, in the periphery dose errors can reach 100% and more. The use of erroneous dose data (see Figure 1) can lead to wrong risk estimates. Therefore a lot of effort is undertaken to produce precise dose computations in the whole patient volume about which is reported. Strategies are discussed how to include relevant dose information into cancer registries.

The association between radiation exposure and cancer risk has been studied for several decades, although in the clinical oncology setting, significant gaps in the understanding and management of radiation therapy (RT) related second cancer risks still exist. This talk will address the clinical implications of current knowledge relating to treatment-related second cancers, including:

1. Treatment selection: Some clinicians or patients may opt to avoid RT in order to reduce the risk of second cancers. These decisions often reveal important misunderstandings about the impact of age, competing risks of death or other morbidity, and differences between absolute and relative risks. Through a case-based approach, participants will learn to identify scenarios in which over- or under-estimation of second cancer risk may lead to suboptimal treatment choices.

2. Modification of Radiation Treatment: Oncologists are able to deliver dose much more precisely than ever before, but it remains difficult to decide where to deposit excess dose, or if low doses to large volumes are more carcinogenic than high doses to small volumes. The emergence of proton therapy now adds further complexity to these issues. In this session, participants will learn about dose-risk relationships and the clinical implications for radiotherapy planning.

2. Clinical management in follow-up: Survivorship care is of growing clinical concern, and management of second cancer risk is an important feature of this care. Oncologists will be required to have familiarity with guidelines recommending specific screening interventions following RT. Participants will learn about resources and guidelines for management of second cancer risk, and the evidence supporting these guidelines will be reviewed.

**SP-0438**

**Clinical implications of secondary cancer risks in pediatric and adult patients**

D. Hodgson1

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**Proffered Papers: Radiobiology 4: Molecular biomarkers for patient selection**

**OC-0439**

**Localization of p16 expression is an important factor to determine radiotherapy response in HNSCC**

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**Purpose or Objective:** The influence of HPV positivity on therapy response in head and neck squamous cell cancers (HNSCC) highlights the importance of uniform and robust biomarkers for stratification of HNSCC patients. Our previous report indicates that p16 is not only a surrogate marker for HPV infections but has an active role in modulation of radiotherapy response by impairing DNA damage response and repair, which is a process known to be dominant in the nucleus of the cells. Based on this, we hypothesized that p16 compartmentalization according to nuclear and cytoplasmic expression may have a role in risk stratification.

**Material and Methods:** p16 expression (immunostaining) and HPV status (GP5+/6+ PCR) was assessed in 241 pretreatment biopsies of oropharyngeal cancer patients treated with chemoradiotherapy. Tumors were classified in nuclear p16 expressing (>10% of tumor cells), cytoplasmic (>10% tumor cells) and p16 negative groups. Statistical analysis was performed to assess the correlation between clinical and tumor characteristics and p16 immunostaining. Influence of p16 localization on radiotherapy response was further assessed by clonogenic and cell survival assays in HPV/p16 negative HNSCC cells transfected with viral construct containing p16-NLS (nuclear localization signal); p16-NES (nuclear exit signal) and p16-WT. The expression and localization of p16 was confirmed by western blotting and immunofluorescence. The response of p16 localization on DNA damage response and homologous recombination repair (HRR) was assessed by gH2AX, RAD51 foci formation and immunoprecipitation.

**Results:** Nuclear p16 expressing HNSCC showed significant (p<0.05) better locoregional control rates (5-year 82%) compared to cytoplasmic p16 positive (5-year 55%) and p16 negative patients (5-year 48%). Only nuclear p16 expression was a significant prognostic factor for locoregional control with a hazard ratio of 0.48 (p<0.05; 95% CI: 0.22-1.01). Interestingly, HPV positive patients were significantly enriched in the nuclear p16 expressing group (60%) compared to cytoplasmic p16 expressing group (9%). In concordance with our patient data, cells containing nuclear p16 expression (p16-NLS) showed a higher radiosensitization compared to cells with predominant cytoplasmic p16 expression (p16-NES).