iferences in the bladder area.

A number of feature-based approaches are used like the Finite Element Method (FEM). The FEM describes the forces in the bladder and deformations the organs according to urine filling by solving the stress equations. Such models are in principle able to yield a good anatomical correspondence. However, for their best performance they require detailed knowledge of the tissue properties which is not yet available.

A more heuristic approach can be followed by application of the Symmetric Thin Plate Spline Robust Point Matching algorithm. Points are placed on the surfaces of the volumes that have to be matched. Subsequently, the distances of these points are minimized. Recently, the algorithm is modified with a weight parameter to allow flexibility control of the tumor and bladder wall. They are considered as separate structures, with a more flexible bladder. Rather coherent registrations are achieved, with fewer marker errors for the modified algorithm (Figure).

It can be concluded that important progress has been made to effectively improve bladder cancer irradiation. An important role is played by the cystoscopic guided tumor demarcation to visualize the tumor during treatment. Sparing of normal tissue is achieved by the adaptive procedures. Improvements have to be achieved for better practical support of clinical ART procedures and deformable image registration for accurate dose accumulation.

Figure Visual representation of non-rigid registration results for one example case, illustrating the effect of several methods. Translations are applied to the lipiodol spots. Planning bladder (grey) is registered to the bladder in repeat-CT (pink) and the resulting transformation is applied to sampled surface points of lipiodol spots. \( w \) refers to relative bladder weight for the non-rigid match.

a) Original position of the lipiodol spots after bone match. b) S-TPS-RPM registration of bladder alone. c) w-S-TPS-RPM registration with \( v=0.8 \).


SYMPOSIUM: NORMAL TISSUE TOLERANCE: THE LESSONS OF POPULATION-BASED APPROACHES

SP-0023

Large cohort studies on late effects of childhood cancer
J.F. Winther

By using the unique resources for conducting epidemiological research that we have in the Nordic countries, facilitated by the existence of nationwide population and health registries that can be accessed with unique individual identification numbers, several population-based studies have been conducted within the Nordic countries to evaluate the impact of cancer therapy at a young age on the health of the patients and their offspring. Three different population-based, nationwide studies will be presented as examples of clinical epidemiological studies on late effects of childhood cancer with outcome data derived from health registries and a ‘gold standard’ approach being used for exposure assessment including organ radiation dosimetry: (1) A case-cohort study based on the population-based cohort of Danish childhood cancer patients and all their children with the purpose to quantify the extent to which cancer therapy contributes to genetic disease in the children of survivors including chromosomal abnormalities, congenital malformations, stillbirths, and neonatal deaths as possible indicators of genetic damage in the next generation. Preconception radiation doses to the gonads, uterus and pituitary gland and administered chemotherapy may have been quantified from medical records and related to adverse outcomes using a generalized estimating equation model and the results will be presented. (2) A greater international collaboration to study trans-generational effects of cancer treatment in children and adolescents - the Genetically Exposed Offspring of Childhood Cancer (GEOPCC) study - currently under way in Denmark, Finland and the USA with a similar design but with an increased sample size by adding the offspring of cancer survivors diagnosed in early adulthood in both Denmark, and Finland (www.geopcc.org). This study is expected to provide more definitive answers to questions about the integrity of the germline in human populations that have been exposed to mutagenic cancer therapy. (3) A large ongoing Adult Life after Childhood Cancer in Scandinavia (ALiCCS); www.aliccscs.org study of late effects in childhood cancer patients. The Nordic cohort consists of nearly 33,000 children and adolescents with cancer diagnosed below age 20 in Denmark, Finland, Iceland, Norway, and Sweden. Morbidity-specific incidence and cause-specific mortality in these patients will be compared with that of a combined Nordic cohort of more than 212,000 population-based comparisons. In a cohort surveillance approach, the relative and absolute risks for different chronic diseases in adult survivors will be assessed based on discharge diagnoses in national population registries. In the initial phase of this research project, priority is given to late effects in terms of cardiovascular and pulmonary disorders, endocrine disorders and reproductive failures, and renal and gastrointestinal disorders. Based on the findings in this screening phase, specific, well-defined outcomes will be investigated in case-cohort studies among 5-year survivors in order to investigate associations, including dose-response, between specific treatment regimens and selected outcomes. Detailed information on chemotherapy including drugs and dose and radiotherapy will be abstracted from medical records and for some of the studies organ radiation doses from direct and scattered irradiation will be estimated. The strengths of these studies include the unbiased ascertainment of cancer cases through a search in nationwide cancer registries, complete identification of their children and their offspring, unbiased identification of population comparisons, and long-term, virtually complete follow-up of all study populations.

SP-0024

Questions in radiotherapy and answers from late effects population studies: Proposed approaches to bridge the gap
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Adverse effects of cancer treatment (normal tissue damage, new malignancies) represent well-studied phenomena across the different disciplines. Novel steps are needed to fully exploit current technical opportunities to avoid normal tissue radiation exposure. Pediatric oncology represents a good model to illustrate the proposed approaches. On average pediatric cancer patients have a better prognosis compared to adults, they are treated to radiotherapy and chemotherapy during vulnerable periods of growth and development, treatment field delineation can be challenging due to close proximity of surrounding organs in small children, and these patients are at potential risk for a variety of health problems at different points in their life span. Valid dose effect studies require accurate characterization of radiation dose characteristics combined with complete and accurate follow-up for health effects, including uniform definitions for such health outcomes. In the past, collaborative groups of pediatric oncologists, epidemiologists, and radiation oncologists have initiated large observational follow-up studies of cancer survivors, to quantify dose effect relationships for chemotherapy and radiotherapy. The professionals who treat childhood cancer patients typically follow trial protocols, thus allowing for large, often international, trial based late effects follow up studies. These studies seemingly represent rather separate, parallel efforts, often using different terminology but seeking answers to closely related or identical questions. From a methodologic perspective, trial based follow-up efforts are based on excellent dose assessment methods but face challenges in achieving uniform and complete health outcome follow-up beyond 10 or even 5 yrs post treatment. Conversely, observational retrospective follow-up studies typically have reasonable or good health outcome data coverage spanning 30+ yrs of follow-up for the oldest pediatric cancer survivors, however, it has remained challenging to accurately describe doses at organs at risk according to the standards common (and expected) in clinical radiation oncology. In essence, we need to combine the dose estimation standard from clinical trials with the follow-up methods applied in observational studies. Several parallel approaches should