Material and Methods: Our cohort includes 15 pts (6 girls, 9 boys) treated with RT for HL, in age 6-25 years (median 17) at the RT, from 2008 to 2013. The 15 pts are representative of different RT target volumes (e.g., bilateral neck, ipsilateral neck, mediastinum, mantle-field, lombo-aortic and spleen, inverted Y, inguinal field, or a combination of them). We calculated the excess absolute of risk (EAR) end the cumulative risk of “all solid” and “single organ” SMN: mouth and pharynx, parotids glands, thyroid, lung, stomach, small intestine, colon, liver, cervix, bladder, brain and spinal cord, skin, female breast, bone and soft tissue. Every HT plan has been compared with 3D-CRT plan, both for EAR, cumulative risk and target coverage.

\[
E_{\text{A}} = \frac{1}{V_t} \sum_i V(D_i) \beta_{\text{A}} RED(D_i) \mu(\text{age}, \text{age})
\]

Results: The risk of SMN solids is high, for both techniques, for breast, lung, thyroid, skin and colon. Some HT treatments may lead to increased risk of SMN solid than 3D-CRT plans, depending on the patient’s age at exposure, on the specific organ volume or target volume and on the dose-response of each site. All the HT plans have the best conformation to the target and the greatest homogeneity of the dose to it delivered (best conformation number and homogeneity index).

Conclusion: Even if HT increases the target coverage in all pts, it could increase the incidence of SMN compared with 3D-CRT plans, depending on single specific target, target volume and pts age. However, EAR estimates are affected by large uncertainties and more works should be performed to better understand the risk of SMN with modern RT techniques after a childhood cancer.

Symposium: QA in clinical trials: processes, impact and future perspectives

SP-0231
How effective is current clinical trial QA?

E. Miles

1Mount Vernon Hospital, Academic Physics, Northwood Middlessex, United Kingdom

A central independent quality assurance (QA) process is acknowledged as an essential component of current radiotherapy clinical trials. QA processes are implemented both pre accrual and during accrual. The former ensures centres have the equipment, expertise and ability to comply with trial protocol requirements and that they are able to deliver treatment accurately and consistently. During accrual processes assure continued compliance and consistency of treatment delivery both within individual centres and across all recruiting centres throughout the trial. The key process areas in QA activity are:

- Target volume and organ at risk outlining
- Treatment planning and optimisation
- Treatment delivery and verification
- Dosimetry Audit

This talk will focus on the following main themes expanding on the processes involved and providing evidence and examples from individual trial QA programmes.

The implementation of clinical trial QA: Appropriate QA tasks to include questionnaires, process documents through review of example patient cases to dosimetry audit site visits, are assigned on an individual trial basis. The level of QA required will vary according to the complexity and novelty of the radiotherapy technique.

Defining standards: It is well recognised that target volume and OAR delineation and treatment planning and optimisation may be variable and open to individual interpretation. Through multi professional trial workshops, provision of delineation guidelines and setting of dose-volume constraints, consensus benchmark standards can be defined.

Assessment against a benchmark: Conformity metrics and pre-defined mandatory and optimal dose constraints can be used to review against consensus standards to highlight potential protocol variations. Historically this review has been retrospective; however increasing use of prospective evaluation with constructive feedback can allow correction of protocol variations before treatment is delivered.

Verification of treatment delivery: Dosimetry audit in the form of a postal or site visit serves to provide an independent assessment of dose delivered and directly compares individual centres. Recently, resulting from advances in image guidance, adaptive radiotherapy has been introduced in the clinical trial setting, introducing new challenges in assessment of plan selection competency and compliance.

As more advanced technology is introduced in the clinical trial setting, QA activities must continually evolve to provide a safe framework for implementation of technical radiotherapy. Increased participation in clinical trials demands a streamlined approach to QA to reduce workload, improve efficiency and facilitate opening centres for recruitment earlier. Participation in a comprehensive QA programme not only accredits the centre for recruitment but also benefits the general standard of RT delivered.

SP-0232 How does QA impact on clinical outcomes?

D.C. Weber

1Paul Scherrer Institute PSI- Center for Proton Therapy- ETH Domain, Radiation Oncology, Villigen PSI, Switzerland

Radiotherapy (RT) planning and delivery for cancer management has substantially evolved over the last three decades with lately the introduction of intensity modulated RT, image-guided RT and stereotactic ablative RT to name a few techniques. The evaluation of these high precision delivery techniques in routine care and in clinical trials alike are error prone. They thus do require optimal RT quality assurance (RTQA) assurance programs which aim at defining the range of acceptable variations and importantly developing mechanisms of action for detection and prevention of potential variations. RTQA outside a clinical trial is defined by all processes that ensure consistency of the dose prescription and the safe delivery of that prescription with regard to dose to the target and critical structures, minimization of the exposure of the RT personnel. In the framework of clinical trials assessing the efficacy of RT with or without a combined modality, RTQA is also necessary to avoid the corruption of the study-endpoint, as RT variations from study protocol decrease the therapeutic effectiveness.
and/or increase the likelihood of radiation-induced toxicities. Prospective trials have shown that RTQA variations have a significant impact on the primary study end-point and could bias the analysis of the trial results. A large prospective phase III (i.e. TROG 02.02) trial showed indisputably that poor radiotherapy resulted in suboptimal patient’s outcomes. Moreover, the impact of poor quality radiotherapy delivery exceeded greatly the benefit of chemotherapy, thus biasing the primary end-point of this study. This large Australian trial provided a contemporary benchmark that future studies will need to exceed. Other specific consideration for RTQA in trials includes, but is not limited to, education of the accruing sites in RT-trial guidelines, promotion of consistency between centers and estimation of inter-patient and inter-institutional variations. Additionally, global cooperation is essential in the environment of common and rare cancers alike, in order to be able to create sufficiently large patient data sets within a reasonable recruitment period. This cooperation is not without issues and recently the need to have harmonized RTQA procedures has been strongly advocated by the Global Harmonisation Group. Ensuring RT compliance with protocol guidelines involves however gradually more resources-intensive procedures which are also labor intensive and are not cost-neutral. This will consequentially have a significant impact on the overall study budget. There are suggestion that QA programs are however cost-effective. This financial investment is of paramount importance, as non-adherence to protocol-specified RT requirements in prospective trials is very frequent. The European Organisation for the Research and Treatment of Cancer (EORTC) Radiation Oncology Group started to implement RTQA strategies in the 1980s, including on how to write a protocol for RT trials, defining RTQA procedures (such as benchmark case, dummy run and complex treatment dosimetry checks), assuring prospective individual case review feasibility and implementing an electronic data-exchange platform.

Keywords: Quality assurance, RTQA, prospective trial, patient’s outcome, toxicity

SP-0233 What will we need for future RTQA in clinical trials?
C. Hurkmans
Catharina Ziekenhuis, Eindhoven, The Netherlands

A trial protocol with clearly established delineation guidelines and dose-volume parameters is key to all RTQA. Acceptable and unacceptable variations thereof should be defined before the trial starts as these are the standards to which all RTQA data collected will be compared. The experience so far has been addressed by the previous two speakers. Dr. Miles presented the RTQA procedures in clinical trials, different protocols, and RTQA review organisation, including anonymisation software, definitions of acceptable and unacceptable variations. Thereafter, Dr. Weber clearly showed that non-adherence to protocol-specified RT requirements is associated with reduced survival, local control and potentially increased toxicity. Thus, it can be concluded that clinical trial groups have established RTQA procedures and conformance to these procedures strengthen the trial results. In this talk the remaining issues that need to be solved will be addressed. These issues can be separated in:

1. How can we further optimising the current RTQA procedure?
2. How should we include new imaging and treatment modalities in our RTQA program?

The first part of the talk will address several initiatives to further optimise current RTQA procedures. As we have learned from past RTQA experience, currently the individual case reviews (ICRs) are the most common source of variations from trial protocols. ICR variation is also the most important RTQA factor affecting trial outcome. Thus, a transition is needed from retrospective ICRs to timely, full prospective ICRs. Also, with the further advancement of tailored treatments for small subgroups of patients there is a growing need for intergroup trials to increase the accrual rates when conducting trials for such patient groups. These changes place new requirements on multiple parts in the RTQA procedure:

- Standardisation of RTQA across various trial groups. The Global Harmonisation Group initiative.
- Standardisation of protocol requirements with clear definitions of acceptable and unacceptable variations.
- Standardisation of OAR and target naming conventions.
- Automated upload of RTQA data from institutions to the RTQA review organisation, including anonymisation software, use of Dicom standards.
- Metrics and software tools to automatically evaluate image quality, delineations and treatment plans.

The second part of the talk will address the ideas of including new diagnostic, treatment and evaluation modalities and techniques in RTQA programs. Examples will be shown of RTQA trial procedures for breathing correlated 4D-CT, 4D PET-CT, MRI and CBCT currently in use or under development.

Proffered Papers: Radiobiology 3: Novel targeting approaches in combination with radiation

OC-0234 Radiotherapy and L19-IL2: perfect match for an abscopal effect with long-lasting memory
N.H. Rekers1, A. Yaromina1, R. Biemans1, W.T.V. Germeraad2, D. Nerl1, L. Dubois1, P. Lamin1
1MAASTRO, Department of Radiation Oncology, Maastricht, The Netherlands
2Maastricht University Medical Centre, Department of Internal Medicine, Maastricht, The Netherlands
3Swiss Federal Institute of Technology, Department of Chemistry and Applied Biosciences, Zurich, Switzerland

Purpose or Objective: There is conclusive evidence that radiotherapy (RT) can initiate an immune response. Previously, we have shown that addition of L19-IL2 to RT was able to increase the immune response and that this combination therapy resulted in a long-lasting synergistic anti-tumor effect. Here we hypothesize that tumors outside the radiation field will also be eliminated by this combination treatment (abscopal effect) and that tumors cannot be formed again after re-challenging cured animals (memory effect).

Material and Methods: Immunocompetent Balb/c mice were subcutaneously injected with syngeneic colorectal C51 cells in both flanks at different times. Primary tumors were irradiated upon a volume of 200 mm³ (15 Gy or 5x2 Gy) followed by PBS or L19-IL2 administration and the growth of the secondary non-irradiated tumors was monitored. Cured mice were re-injected after 150 days with C51 tumor cells and tumor uptake was assessed. Several immunological parameters in blood, tumor, lymph nodes and spleens were investigated in both experiments.

Results: RT+L19-IL2 was able to cure 100% of primary tumors and was associated with an increased percentage of CD8+ T cells inside these irradiated tumors. When a single RT dose of 15 Gy was combined with L19-IL2, 20% of the non-irradiated secondary tumors were cured. Interestingly, the non-irradiated tumors of mice treated with 15 Gy+L19-IL2 showed a significant (p<0.01) increased percentage of CD4+ T cells compared to irradiated tumors. Fractionated radiotherapy combined with L19-IL2 caused a significant (p<0.01) growth delay in the non-irradiated tumors, however no secondary tumors were cured. Immunological analysis revealed an increase in PD-1 expression on T cells infiltrating these tumors, suggesting a more regulatory phenotype after fractionated radiotherapy compared with one single RT dose. New C51 tumors were not able to form in cured mice whereas 100% of the age-matched control mice formed tumors that reached established end-points within 17 days. Splenic T cells of these cured mice were associated with a high expression of CD127.

Conclusion: Our data show that RT+L19-IL2 causes anti-tumor immune effects outside the radiation field and this effect is associated with an increase of CD4+ T cells. Cured mice are