TEACHING LECTURE:

SP-0373
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Rationale:

The incidence of anal cancer in the general population has increased over the last 30 years although it remains a relatively rare entity. A number of clinical trials conducted in the 1990’s, showed that radiotherapy combined with chemotherapy can cure the disease in the majority of patients whilst preserving the anal sphincter. Trials that investigated chemotherapy combinations failed to improve over the current standard combination of mitomycin-C and 5-FU. However, different radiation strategies and schedules were used in the various phase II and phase III trials (that primarily addressed chemotherapy questions), we performed a pooled analysis of the data from all available phase II and III trials in to identify radiotherapy related parameters affecting the outcome of patients with anal cancer, resulting in new and improved guidelines for future studies and for tailor-made treatment.

Methods: A total of 13 trials (7 phase II and 6 phase III) conducted were identified, totaling 3227 patients recruited between 1986 and 2010. Data from 3036 patients from 10 studies were received (94.1%). Of these studies, 3 were conducted before 1994 and randomized against radiation alone or combined with SFU only. These studies were excluded from the main analysis which focuses on radiation combined with doublet chemotherapy (N=2033). Patients not >75 years, not MO, or T1N0 were excluded, as well as all patients treated by brachytherapy, those who received <40 Gy of treatment (considered unfit) leaving 1343 patients in the analysis. The primary endpoint is local-regional control within 5 years of entry on study. Local-regional failure included events of local or regional failure and the need for local surgery. Secondary endpoints were progression-free and overall survival. A cox model adjusted by patient and disease factors was fitted to study the impact of treatment dose and duration. Statistical significance is claimed at the 5% level.

Results: The radiotherapy regimens used in the studies are described in Table 1.

Two third of the 1342 patients were women; the median age was 56 years (range: 25-75). Tumor was confined to the anal margin in 82 patients (6.1%). The median tumor size was 4.1 cm, 64.1% of the patients had T. The median follow-up in the studies was 4.1 years. By year 5, a total of 303 events of loco-regional failure were observed with 5-year cumulative incidence of 25.1% (95%CI: 21.9-28.3%). The model included effects for sex, age (in years), N stage (N+ inguinal nodes -, N+inguinal nodes -, N+ unknown inguinal status vs N0), tumor localization (anal canal vs anal margin only), tumor size in cm (within combinations of tumor location and N category), total dose on the anal canal (<50.5 Gy vs >50.5-55 Gy, >55-59 G, >59-59.4 Gy, >59.4 Gy) and overall treatment time within defined dose. This model shows a statistically significant negative impact of tumor size (P=0.0086) and of prolonged overall treatment time (P=0.0126). When the overall treatment time is split between the duration of the gap and the duration of the effective treatment time only the duration of the gap remained statistically significant (P=0.0049) whether the effective duration of the treatment lost statistical significance (P=0.0786).

SP-0374
Notch signaling: prospects on cancer diagnosis and treatment
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Notch signaling is a highly conserved short-range cell-cell communication pathway that regulates many aspects of embryonic development as well as cell renewal and maintenance of adult tissues. In humans there are 4 Notch transmembrane receptors that are activated by cell surface ligands on adjacent cells of the Delta and Jagged families. Upon ligand binding, Notch receptors are cleaved by g-secretase, releasing the Notch intracellular domain (NICD) that migrates to the nucleus and controls the expression of numerous genes.

Notch is aberrantly expressed in many cancers and both activating as well inactivating mutations are found. Notch signaling is not only important for cancer cells but also required for tumor angiogenesis. Thus, Notch inhibition is an attractive therapeutic target as it could target both tumors and their microenvironment simultaneously. Drugs that inhibit Notch activation such as g-secretase inhibitors (GSIs) are currently in clinical development.

Here I will present an introduction on the Notch signaling pathway its involvement in cancer development and the promises and pitfalls of Notch as a drug target for therapeutic intervention in cancer.

SP-0375
Risk management
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Risk can be defined as a possibility of harm or damage and this is certainly applicable to risk in radiotherapy with potential harm to patients or staff associated with so many of our routine procedures. Risk is a therefore a fact of life in radiotherapy, it cannot be eliminated but it can be minimized by good management. Management is defined in the Oxford dictionary as the process of dealing with or controlling people or things. When we link the two together then we see that what is important is acknowledging the risk, identifying the areas of most significant risk, the factors contributing to the risk and the continuously considering ways in risk can be minimized or eliminated - creating a safety aware culture.

Risk management in radiotherapy has gained significant momentum in recent years partly as a result of the high profile incidents that have been reported in the media. Patients have a right to expect high quality treatment delivered in a safe environment. The negative publicity generated by the media articles greatly enhances fear amongst the general public and our patient population and we have a moral and ethical responsibility to actively address the risks associated with our discipline and to create an environment of openness and transparency surrounding risk and how it is managed. It is important to remember that most errors or incidents are minor but reflect a real opportunity for learning and this is the basis of voluntary reporting systems. An incident reporting system, or safety information system, is one way of demonstrating transparency and a department that puts safety as a priority and is engaged inactive learning. Voluntary reporting systems exist locally, nationally (PRISMA in The Netherlands) and internationally (ROSI and the newly developed International Atomic Energy Agency SAFRON system). Integration of incident and near incident reporting systems have been integrated into safety management programmes in many centres. Professor Jan Willem Leer in Quality and Safety in Radiotherapy
describes the Dutch charter on a safety management system that sets out to perform a regular risk inventory, create a system for blame-free reporting, develop a system for data analysis and to put a system in place for implementation of improvements.

However incident reporting is only one element of risk management and should be seen as a tool to facilitate analysis and identify where change will be most effective. A range of methodologies can be used to assess and manage risk including Failure Mode and Effects Analysis (FMEA), Root Cause Analysis (RCA) Events and Isuas Factors Analysis (ECFA) and incident reporting, investigation and analysis. Methodologies can be simple or very complex and are applicable in different settings but basically involve identifying factors that have led or could lead to incidents occurring and considering strategies to manage these factors. It is also necessary to consider the organization and the environment in which radiotherapy is prepared and delivered and the personnel involved as these can also contribute to risk. As systems become more complex they become less transparent with greater opportunity for incidents to occur. Analysis of the functioning of the organization and its personnel can be facilitated by regular audit identifying risk areas. Risk management should be seen as a proactive process designed to improve quality by reducing risk and the number of incidents that occur in our departments. Incident reporting and analysis is of no benefit without feedback and involving all appropriate staff in addressing the findings and implementing change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change.

For printed versions, SP-0376, SP-0377 and SP-0378 are not available.

**Discussion**

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Support with research and education. Finally risk management is effective when a strong safety culture exists that is actively addressing the findings and implementing change. It is the goal to improve quality by reducing risk and the number of incidents that occur. Analysis of the functioning of the organization and its personnel can be facilitated by regular audit identifying risk areas. Risk management should be seen as a proactive process designed to improve quality by reducing risk and the number of incidents that occur in our departments. Incident reporting and analysis is of no benefit without feedback and involving all appropriate staff in addressing the findings and implementing change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change. It is the responsibility of all professionals involved in the process, to share its findings and implement change.

**Orientation.** A thorough way of getting oriented is to explore every possible direction and see where it leads. In dose optimisation, each exploration requires a full dose optimisation and is hence time consuming. To work around this, navigation tools have been devised that rely on a set of pre-computed dose plans, and much effort has been devoted to reducing the number of these computations. An alternative within the framework of constrained optimisation is sensitivity analysis, which estimates the change in one cost function if another one is altered (i.e. the slope of the tangent to the Pareto frontier). This does not require pre-computation, but is restricted to small changes and hence relies on a good start location. Arriving: No amount of information can avoid that the route to the final choice is a repeated cycle of getting directions and taking a step, especially when the number of competing objectives is large. Later steps could partially invalidate previous ones. Therefore, it becomes essential to treat already established cost function values as constraints. Besides for navigation “on foot”, constrained optimisation is also the key to various methods of automated route finding (i.e. proper simultaneous optimisation of multiple criteria) like lexicographic ordering or constraint prioritization. These methods combine the trade-offs the expert would usually employ and apply these rules in an attempt to perform at least the most obvious selection steps unsupervised. Although multi-criteria algorithms are built on mathematically rigorous formalisms, the concepts derive their value from their interactive usability and the users’ preference, and are therefore ultimately subjective.

**Accessibility.** The term “Pareto frontier” has become known for the set of all competing solutions of a dose planning problem. The compromise, and even the existence of this Pareto frontier is trivial in the general setting of dose planning, which is why usually only fluence distributions or idealized dose distributions (instead of deliverable plans) and physical cost functions (instead of dose-volume and some biological cost functions) are considered. Under these conditions, each point of the Pareto front can be reached by an unconstrained dose optimisation with a specific priority weight for each cost function. A more direct alternative is to turn all but one cost function into constraints and employ constrained optimisation, which also remains viable in the more general setting.

**Discussion**

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Over the last few years, positron emission tomography (PET) has proved to convey useful information for treatment planning in radiotherapy. Within this framework, the most straightforward way to exploit this information is to use PET images to delineate the target voxels. However, PET images are blurred (positron annihilations are difficult to locate in wide gantries and in attenuating material) and noisy (annihilation counts are low). Noise is generally attenuated by smoothing the images even more heavily. By essence, blur complicates the segmentation problem, as it increases the uncertainty about the location of the target edges. Other, secondary causes have a methodological nature and result from the first one. Most segmentation methods stem from very simple or very heuristic models that approximate roughly or even ignore the aforementioned effects, leading to inaccurate results. On the other hand, more complex methods are hindered by an over-fitting effect: they perform well on data they have been calibrated or trained with but they generalize poorly to other images, other cameras, models, etc. This leads us to the third impediment, which is the difficulty of validating the candidate methods on sufficient and appropriate data. In particular, robustness and reproducibility depend on the availability of a large number of images, covering most of the experimental domain, in terms of tumor sites, target sizes and shapes, camera models, etc. Each image should also come with a ground truth