The general aim of variable selection is to arrive at the most parsimonious model, i.e., the simplest model that accurately describes the data. There are several arguments for this principle, including Occam’s razor, interpretability of the resulting model, and to avoid overfitting. The general aim of variable selection is to arrive at the most parsimonious model, i.e., the simplest model that accurately describes the data. There are several arguments for this principle, including Occam’s razor, interpretability of the resulting model, and to avoid overfitting.

In the process to determine which model is the most parsimonious, several combinations of model variables need to be considered. Usually, the total number of possible combinations is too large to evaluate them all. Therefore, stepwise methods have been developed, which come in two flavours: forward procedures, which start with an empty model and iteratively add variables, and, backward procedures, which start with a full model, including all variables, and iteratively remove variables. Both procedures have their benefits and drawbacks. For example, if few candidate variables are considered, the backward procedure is better suited to select predictive combinations of interrelated factors. If many candidate variables are considered, however, the forward procedure is faster and less sensitive to overfitting problems. Also, stepwise methods that combine forward and backward approaches have been developed.

Besides the step direction, the key element in stepwise methods is the criterion that determines which of the compared models is to be preferred. Usually, the likelihood ratio test, the Wald test, the Akaike Information Criterion (AIC), or the Bayesian Information Criterion (BIC). Recently, more accurate criteria based on numerical resampling techniques, such as cross-validation and bootstrapping, have been developed. A completely different approach is taken by penalized methods. The idea of penalization originates from the observation that overfitted models tend to have large coefficients. Therefore, overfitting can be avoided not only by reducing the number of variables in the model, but also by restricting the amplitude of the model coefficients. The LASSO method aims to do both simultaneously, without stepwise procedure. The models found with LASSO generally include more variables than with stepwise methods, but with smaller model coefficients.

Variable selection methods are not limited to logistic regression analysis. The field of machine learning embraces many alternative modelling methods that include variable selection. However, logistic regression is well known, simple, and widely applicable, and therefore, often a first choice. The use of variable selection methods, however, is generally plagued with problems that cause the resulting models to be less reliable than they first appear. Firstly, overfitting is generally not completely avoided by variable selection, such that the resulting models need to be corrected for optimism. Secondly, large model uncertainty often remains, resulting in model instability, i.e., small changes in the data result in largely different models. Thirdly, the models are data-driven, and, therefore, not guaranteed to generalize to populations other than that of the training data. Fourthly, observed associations are not guaranteed to reflect causal relationships. Active internal and external model validation can help to identify and reduce these problems.

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Advanced methods for 2D/3D dose map correlation in modelling toxicity
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Voxel-wise methods based on dissimilarity measurements between dose distributions were recently implemented to describe spatial effects in both the onset of toxicities and the risk of local relapse. These approaches generally employ elastic registration to deform patient images and dose distributions onto one or more patient frames, and are combined with voxel-by-voxel analyses in order to test differences between groups (e.g., patients with/without toxicity).

The different approaches developed or under development have in common the intriguing characteristic to be able to identify sub-regions within an organ at risk (or of organs/structures within an apparatus or a group of organs/structures) that may better discriminate patients with/without toxicity, enhancing in this way more sensitive sub-structures/organs. As a consequence, these approaches could hugely increase the potential of modelling dose-volume effects of specific toxicities by the integration of spatial dose descriptors, helping radiation oncologists in abandoning, when convenient, the concept of homogeneous sensitivity of...
an organ as implicitly supposed by classical NTCP models based on DVH evaluation. Due to the large inter-patient variability of internal anatomy and specifically of largely deforming organs, the generation of common frames permitting to correlate local doses received by different patients is challenging. In the case of hollow organs having an anatomical structure that may be considered in first approximation “invariant” with respect to the surrounding organs, the approach may be simplified by looking directly to the dose-surface map (DSM). This could be the case, for instance, of rectum, bladder, esophagus and oral cavity (mucosas).

Regarding bladder, a new method using pixel-wise correlation was developed and applied to correlate DSM and urinary toxicity. DSMs of patients included in a prospective study (DUE01) were generated by virtually cutting bladder contours at the points intersecting the sagittal plane passing through its centre-of-mass. DSMs were recalculated with a cranial-caudal resolution of 1mm; then, they were normalised in the axial direction and aligned at the bladder base, at the posterior central point, generating a common frame for all patients. Average DSMs of patients with/without toxicity could be compared pixel-by-pixel through two-sided t-tests: the resulting p-value maps identified regions better discriminating patients with toxicity. The method was applied to 79 patients with none/mild urinary symptoms before radiotherapy (assessed as an IPPS value ≥ 15), treated with daily image-guided moderately hypo-fractionated (2.5-2.65Gy/fr, 70-74Gy) Tomotherapy; the end-point was patient-reported urinary toxicity at the end of therapy (defined as IPPS ≥ 15, n=27/79 and focusing on four patient-reported moderate/severe symptoms: frequency n=15, urgency n=10, weak stream n=17, nocturia n=15). DSMs of patients with/without toxicity were significantly different for all end-points, excluding weak stream. The % surface receiving >50-70Gy at 5-7 mm from the base well predicted IPPS ≥ 15 (ORs:1.03-1.07, see Figure). Interestingly, different patterns could be recognized for specific symptoms: a quasi-threshold effect on the absolute posterior dose at 5-12 mm from the base was found for frequency and urgency (ORs:1.52-1.77). This last result was consistent with a previously reported higher sensitivity of the bladder trigone. The method was proven to give relevant additional information on the impact of the shape of the dose distribution within a specific organ and promises to find important applications in investigating urinary toxicity as well as to be potentially applied outside the bladder case.

Radiotherapy is an integral part of breast conserving therapy. It substantially improves treatment efficacy by decreasing local recurrence rates and results in an increased breast cancer specific survival. With the introduction of the planning CT-scan over the last decade, it was possible to gather more precise information on both dose homogeneity in the target volume and mean and maximum dose in the organs at risk. In recent years the knowledge concerning the side effects of this radiation treatment has increased further and, amongst others, the effect on the heart has been described. Preclinical and clinical studies suggest that breast cancer radiotherapy is associated with an increased rate of major coronary events. Based on this knowledge, important aspects of the radiotherapy delivery have been changed in order to decrease the dose in the heart. We propose several improvements in order to optimise the radiation treatment after breast conserving surgery.

As stated in literature, identifying and delineating the Clinical Target Volume (CTV) of the glandular breast tissue and the lumpectomy cavity in radiotherapy is perhaps the most important step. It is prone to error because of difficulties in definition and due to differences in perception between observers. Also the definition of the target volumes influences the dose in the surrounding structures. From several studies it appears that adding MR images did not improve the consistency of the delineated volumes. And it was stated that, apart from guidelines, a peer review of the delineated volumes is of importance. For the CTV of the glandular breast tissue the RTT could be trained to delineate this volume, in order to optimize the efficiency of the radiation treatment process. This was found in literature and confirmed in our radiotherapy department as well. We believe that a shift in activities and responsibilities of the radiotherapy team needs to be implemented gradually.

A next step in the radiation treatment process is defining the treatment plan. Several treatment-planning techniques were compared in order to decrease the dose to the heart. We propose to perform a tangential IMRT technique in all patients after breast conserving surgery, regardless of age and size of the breast. By performing a tangential IMRT technique the dose will better encompass the target volume and the dose in the heart and Left Anterior Descending (LAD) coronary artery will be decreased as well. Moreover, when using a tangential IMRT technique no increase in the low dose regions in the normal tissue has been found, as is the case when making use of a multiple beam IMRT.

Finally, adding a breath-hold technique in the radiation treatment of left-sided breast cancer appears to be of importance, since a breath-hold technique significantly reduces the dose in the heart. Over the past few years, several authors carried out studies to evaluate the pros and cons of various breath-hold techniques and these have proven to be easy performable and reproducible. Because of the ALARA (As Low As Reasonably Achievable) principle, and since a threshold dose for the radiation-induced damage to the heart and the heart vessels is unknown, the LAD dose should be as low as feasible in all patients. Therefore, in our institution all left-sided breast cancer patients were treated with a breath-hold technique, without setting an age limit, since 2010. The breath-hold technique we apply is the Active Breathing Control (ABC) technique. After two years, the feasibility of the ABC technique was evaluated: it appeared that 98% of our breast cancer patients were able to undergo the breath-hold technique.

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Contouring/treatment planning aspects (RTT)
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