Current strategies in radiotherapy of head and neck cancer

Abstract

The Intensity Modulated Radiation Therapy (IMRT) together with Image Guided Radiation Therapy (IGRT) improves radiation therapy for head and neck cancer. On the one hand tumors can be better covered with radiation dose and on the other hand normal tissue can be better preserved. Carefully applied this leads to the same tumor control rate with reduced toxicity compared with conventional radiation therapy. Respective to the addition of systemic therapy to irradiation therapy, platinum based radiochemotherapy remains the standard of care and there are first indications, that at least in the primary treatment of head and neck cancer the addition of Cetuximab to a cisplatin-based radiochemotherapy did not improve outcome.

1 Intensity Modulated Radiation Therapy (IMRT)

The goal of radiotherapy of malignant tumors is to deliver a tumor sterilizing dose. In principle it is possible to deliver enough dosage to kill all tumor cells in vitro. The limitation in radiation therapy in vivo is the surrounding normal tissue. It should only get as much radiation dose that the reversible acute toxicity is tolerable with supportive care and the probability for irreversible, clinically relevant late toxicity is low (typically smaller than 5 percent after 5 years, TD5). In this context irradiation therapy is favoured by the fact that the sensitivity of the cells for irradiation of healthy tissue is smaller than that of tumor cells. On the other hand radiation therapy tries to geometrically concentrate radiation dose only to the volume where macroscopic tumor is present or where microscopic tumor is assumed. In the implementation of this goal Intensity Modulated Radiation Therapy (IMRT) is an important improvement over conventional 3D conformal radiotherapy. The term is derived from the variable irradiation intensity over the beams transversal section. With this technique it is possible to irradiate complex, especially concave shaped, targets easier than in the past. So the normal tissue can be better spared and the tumor tissue can be irradiated with a higher dose.

There are different techniques to implement IMRT. The first commonly used and up to date most widely used technique is the “Step and Shoot”-method. When the support shaft of a linear accelerator (gantry) is in a certain position, from this direction several beam segments with different aperture configuration are delivered. Originally irradiation was only turned on when the aperture configuration was fixed in a definitive position. To shorten treatment time the next technological step was to keep irradiation switched on when the aperture was modified (“Sliding window”-method). In the most modern technology the irradiation source stays switched on continuously during movement of aperture and gantry (“Volumetric-modulated-arc-therapy”). By introducing the last two methods a faster irradiation is possible. The delivering time of an IMRT for head and neck cancer could be shortened from 20–30 min for step-and-shoot method to 10–15 min with the volumetric-arc-method. All three so far described methods can be in principle delivered with conventional linear accelerators (“linacs”). Dedicated linacs to deliver only IMRT are for example the TomoTherapy®-machine and the CyberKnife®-system. Here, radiation sources are built in a kind of CT scanner or on an industrial robotic arm. Both are not able to apply conventional radiation therapy methods.

Because of IMRT irradiation volumes can be much more individualized. On one hand this leads to a better protection to the organs of risk. On the other hand there is the danger that with careless use of IMRT a certain region can get underdosage, which would have been irradiated without IMRT anyway. The first studies suggest how the target volumes should be optimized when using IMRT techniques [1]. In principle clinical studies show, that compared with conventional irradiation therapy IMRT can reach the same good results in tumor control [2]. On the other hand the advantages of IMRT by reducing late toxicity especially for tumors in nasopharynx, oropharynx and paranasal sinuses are demonstrated [3, 4]. For these three tumor localizations the use of IMRT is recommended by “National Comprehensive Cancer Network” (NCCN). Clinical trials approved that the better protection of organs of risk, especially the salivary glands, lead to a clinically relevant improvement in late toxicity [5]. But it was also demonstrated, that the correlation between measurable parameters like better rate of salivation and improvement of quality of life is not always straight forward [6].

Figure 1 and Figure 2 show for nasopharyngeal carcinoma how IMRT can be used for the protection of optical structures, brainstem and pituitary gland. Another typical problem of conventional head and neck radiation therapy is the sufficient irradiation of lymph nodes in the neck without damage of spinal cord as a potential source of...
irreversible late toxicity. Figure 3 shows a sophisticated way to achieve this with IMRT without the problem of field alignment. Another example of IMRT in Figure 4 shows how the parotid gland, which is very sensitive for irradiation, can be spared with IMRT. This should lead to a decrease of severe xerostomia, which is frequently combined with a reduction of life quality [7].

Figure 1: Part of a plan to irradiate nasopharynx cancer. It shows how the use of intensity modulated radiation therapy preserves the eye socket/orbita on both sides.

Figure 2: Same part of a plan as in Fig. 1 to irradiate a nasopharynx cancer. It shows that by intensity modulated arc therapy at the same time of preserving the orbitae a sparing of brain stem, optic chiasm and pituitary gland is possible.

Figure 3: Despite of adequate sparing of the spinal cord the level 5 lymph nodes are fully enclosed and sufficiently irradiated by using intensity modulated radiation therapy.

Figure 4: Example for the ability to spare the right parotid gland and to cover the elective lymph nodes with a sufficient dose by using intensity modulated radiation therapy. If there are affected lymph nodes adjacent to the parotid gland it is normally not possible to spare the gland, which is comparatively sensitive to irradiation.

In connection with the modification of the dose distribution by using IMRT the relevance of PET-CT will be defined in the next years. Because of the risk to spare tissue with tumor by modification of volume it seems to be wise to use PET-CTs liberally in target definition for IMRT in the moment. To assure the comparability of trials it is especially important for IMRT to keep standards, e.g., for the CT-based irradiation of lymph nodes in the head and neck region [8].
2 Image Guided Radiation Therapy (IGRT)

By using conventional irradiation therapy with photons the positioning error of patients in the range of a few millimeters was without bigger concern because of adequate safety margins provided by the limited conformality. In CT-based 3D-techniques and especially in IMRT the requirements to patient positioning became more relevant. Traditionally the planned patient position is verified by simulators with kV-beam and by projection of the MV-irradiation beam at the linacs. Both methods compare the position of the patient sol anatomy between planning stage and current position by using conventional projection techniques. An improvement of these methods is on one hand to use three-dimensional visualization techniques. On the other hand techniques with improvement of soft tissue contrast will lead to a better positioning. In the last few years the manufacturer of conventional linacs introduced “conebeam-CT” (CBCT) i.e., a CT at the linear accelerator to achieve this for irradiation therapy of head and neck tumors (Figure 5). In a typical layout of this method an x-ray source is fixed at the gantry perpendicularly to the treatment beam. By rotating the gantry once around the patient in treatment position a CT data file, which contains the whole three-dimensional information for the bones and the soft tissue, can be reconstructed within 1–2 min. The soft tissue contrast is a little bit decreased compared with a diagnostic CT but it is of sufficient quality for positioning of patients according to internal structures. Important structures for guidance in head and neck region like larynx, epiglottis, soft palate or tongue are well definable (Figure 6). Normally the imaging methods for patient positioning are combined with software tools to adjust to a given position, e.g., planning CT (Figure 7). The state of the art systems with appropriate treatment couches (e.g., “Hexapod”) can not only translate along three spatial dimensions, but can adjust rotational errors around the three space axis, too. Generally such systems are called “Image Guided Radiation Therapy” (IGRT). They enable a better and more individualized positioning of patients [9]. A common problem in irradiation therapy of head and neck tumors is that the patients typically lose weight because of problems with swallowing, which is a typical acute toxicity during irradiation therapy. Figure 8 shows that because of this the irradiation mask may not fit precisely to the patients shape anymore. Beside of a decrease in positioning accuracy there is also a change in dose distribution. For this reason in some hospitals patients get a new mask (and together with this a new irradiation plan) at a certain point in time. In other facilities there is made a “clinical” decision if the fitting of the mask is still sufficient. Typically a relevant part of the fixation of the head in the mask is achieved by parts of the head like orbita, nose, zygomatic bone and chin. Because these parts are nearly unchanged by reduction of weight a not everywhere fitting mask may still lead to a sufficient positioning accuracy. Because of the better contrast to soft tissue with CBCT a safe decision can be made about positioning accuracy in the target volume.
situation has two target volumes with a prescription of 50 and 60 Gy. Without IMRT, irradiation therapy is typically delivered in two steps. In the first step 50 Gy are delivered to the large irradiation fields. After that the fields are downsized and 10 Gy are applied to the 60 Gy volume. By introducing IMRT and its special planning systems we get the ability to do so-called “simultaneous integrated boosts” (SIB). In doing so in the same plan a volume with 1.8 Gy single dose and a part of this volume with 2.0 Gy single dose can be irradiated at the same time. After 30 fractions the first volume gets 54 Gy and parts of the volume get 60 Gy. By using SIB the application of irradiation becomes easier and the conformation of dose to the target volume becomes a little better [10].

4 Combination of radiation therapy with systematic therapy

Respective to the agents which are applied in chemoradiation there was no substantial improvement in the last few years. Platinum-based chemotherapy alone or in combination with other agents like 5-FU are still widely used. A new trial about EGFR-antibody Cetuximab in combination with cisplatin-based chemoradiation was published at ASCO 2011 [11]. Comparing cisplatin-based chemoradiation versus cisplatin-based chemoradiation with Cetuximab the addition of Cetuximab in primary treatment does not improve progression free and overall survival. Unaffected of this new trial is the use of Cetuximab together with irradiation in the case of advanced head and neck cancer with contraindication to cisplatin-based chemotherapy and in addition of standard treatment in recurrent disease. However, the higher acute
toxicity of the combination of irradiation therapy with Cetuximab should be balanced to the expected benefit [12], [13], [14].

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