Chapter 7

General discussion

7.1 Introduction
In this thesis intensity-modulated radiotherapy was applied to breast and head-and-neck cancer. In chapter 2 an IMRT technique was developed for irradiation of the breast. A highly conformal dose distribution with a single dose level to the target was obtained. A form of dose painting was achieved for the IMRT irradiation of oropharyngeal cancer. The aim of this treatment was to deliver three dose levels to the target volumes while sparing the normal tissues (chapter 3 and 4). For accurate delivery of the dose distribution, resulting in reduction of the margins needed for geometric uncertainties, the use of gold markers for position verification was investigated for head-and-neck irradiation. Beside interfraction motions, intrafraction motions were determined in the head-and-neck region.
In the next section image-guided IMRT will be discussed in general. A more detailed discussion about the use of IMRT and its implications for breast cancer and oropharyngeal cancer are presented in sections 7.3 and 7.4 respectively.

7.2 Image-guided IMRT
Images providing anatomical and biological data should be available to obtain the ideal radiotherapy plan (Ling et al., 2000). In this thesis CT images are used to visualize the patient anatomy. Using CT scans, electron density information is available, which is needed for accurate dose calculations. Targets volumes and surrounding organs at risk are delineated within the CT images. Accurate delineation of volumes of interest becomes a mayor issue when delivering highly conformal plans with IMRT. When the actual target is larger than the delineated target volume, this results in underdosage in the target and can result in a reduction in TCP. On the other hand, when the actual target is smaller than the delineated
target, this may have consequences for the dose to the surrounding tissues. The
uncertainties in delineation should be taken into account during the planning pro-
cess. In order to estimate the uncertainties and improve the delineation process,
delineation studies are essential. The simultaneous use of different imaging modal-
ities, such as CT, MRI, or PET, could improve the delineation process, because
the advantages of each separated imaging modality can than be combined. The
advantage of MRI is that it can be used to visualize soft tissue. Several studies
reported the used of MRI for delineation of various cancer sites (Rasch et al., 1997,
1999; Weltens et al., 2001; Nishioka et al., 2002; Parker et al., 2003; Ten Haken
et al., 1992). PET has shown to be helpful in detecting lymph node metastases for
lung cancer (Marom et al., 1999; Gould et al., 2002), for the head-and-neck cancer
the use of PET for that purpose is still controversial (Nishioka et al., 2002). PET
can also be used to determine the boundaries of primary tumors when there are
inflammatory changes around the tumor (Nishioka et al., 2002). The combined use
of these techniques should be investigated. Image fusion, the 3D matching of each
image data set, is then of crucial importance.

Using the anatomical data of the CT, the three-dimensional dose distribution can
be calculated by inverse planning based on dose constraints assigned to the delin-
eated volumes (chapter 3 and 4), or directly by using the CT three-dimensional
geometrical information (chapter 2). The use of biological data for treatment plan-
ing is still under development and is not used for treatment planning in this thesis.
Instead, the clinical starting points, i.e. the prescribed dose to the targets and the
tolerance dose of the organs at risk, were based on clinical studies applying ho-
mogeneous dose distributions. Tumor characteristics, such as tumor cell density
and radiosensitivity, however, are not homogeneously distributed throughout the
target. The use of image modalities such as PET, SPECT and MRI, providing
functional information of the tumor, should therefore be investigated. Using this
information it might be possible to improve the TCP by applying a heterogeneous
dose distribution based on tumor characteristics.

During radiotherapy, the position of the target should be the same as during the
imaging process needed for the treatment planning. In this thesis the use of EPIDs
has shown to be a useful tool to determine inter- and intrafraction motions (chap-
ter 5 and 6). Although gold markers can be used for position verification purposes,
there is lack of anatomical information during radiotherapy. Due to radiotherapy,
the shape and size of the anatomy might change. In order to improve the quality
of the treatment, a replanning using the actual size and shape of the target vol-
ume and the surrounding normal tissue could be considered. Other techniques are
than needed to visualize the position as well as the shape and size of the target
volume. A possible way to visualize the target during radiotherapy is the combina-
tion of a linear accelerator and a CT scanner as developed in tomotherapy (Mackie
et al., 1999). Jaffray and Siewerdsen (2000) developed a cone beam CT scanner, by
mounting an X-ray source in combination with a flat panel imager on the gantry
of a linear accelerator. By rotating the gantry a CT scan is acquired. A mobile ultrasound-based targeting system (BAT) has been used for daily verification of the position of the prostate (Lattanzi et al., 2000). Pressure of the ultrasound probe can, however, cause a shift in the prostate location itself (Van den Heuvel et al., 2002), resulting in less accurate position verification of the prostate. The above mentioned systems allow visualization of the soft tissues just before each treatment fraction. An other possible system is proposed by Lagendijk and Bakker (2000). The integration of a linear accelerator and a MRI imager should result in the imaging of soft tissues during radiotherapy.

7.3 Breast cancer

2-field IMRT

Using the three-dimensional geometry of the breast, an IMRT technique was developed (chapter 2). The technique was based on the division of the treatment field in segments with similar equivalent path length through the breast and aims to deliver a homogeneous dose distribution. Several other techniques have been developed based on radiological thickness and transit dosimetry information from EPIDs (Donovan et al., 2000; Lo et al., 2000). In a study of Kestin et al. (2000), segments were designed from isodose surfaces calculated from an open tangential beam. Using these techniques 80% to 90% of the dose is delivered by an open field and 3-8 additional fields are added to create a homogeneous dose distribution. Using a simple dose model Chui et al. (2002) presented a technique where the optimum intensity is obtained by equalizing the dose to the midpoint of pencil beam segments. Others groups used an inverse-planning algorithm, based on dose constraints assigned to delineated volumes, to optimize the dose homogeneity in the breast (Hong et al., 1999; Chang et al., 1999; Hurkmans et al., 2002; Thilmann et al., 2002). Due to the inhomogeneity of the lung, the missing tissue effect and oblique incidence, accurate dose calculation is rather difficult and advanced dose models are required. Dose models used for inverse planning are usually simple compared with models used for conventional three-dimensional planning, in order to achieve acceptable calculations times for the optimization process. This resulted in a significant discrepancy between the dose calculation performed with the 3D planning model and the inverse-planning model used at our department. The inverse-planning module is therefore not used for IMRT for breast cancer until more advanced dose models are incorporated in the inverse-planning module. Most mentioned studies used conventional beam arrangements, i.e. two tangential fields. Using a four-field technique Landau et al. (2001) showed increased dose homogeneity and significant improvement in heart sparing compared to conventional techniques. This resulted, however, also in increased dose to the contralateral
breast, resulting in an increased risk of radiation induced cancer in the contralateral breast (Boice et al., 1992). A six-field arc technique resulted in poorer results than conventionally achieved. Ma et al. (2003) reported that 2-field IMRT could reduce dose to the lung, heart and contralateral breast compared to conventional techniques. Multiple beam angle IMRT resulted in low dose regions in the normal tissues. Furthermore, it was concluded that modulated-electron radiotherapy resulted in high conformal dose distributions. Irradiation with electrons can, however, cause a high skin dose. Li et al. (2000) showed for a combined electron and IMRT technique improvement over the conventionally used tangential fields with reduced dose to the ipsilateral lung and heart dose. A 9-field technique showed similar results for the target coverage, but resulted in increased dose to other normal structures. Thilmann et al. (2002) calculated IMRT plans for various combinations of beams and intensity levels using inverse planning. The optimum treatment plan for a left sided breast consisted of 12 beams using 7 intensity levels. The results were not compared with a 2-field technique, the heart and lung did, however, receive a substantial dose. Overall the two field IMRT techniques seem to have the most benefits. Due to the use of a simple beam geometry, the dose to surrounding normal tissue can easily be avoided, similar to the conventional tangential fields. Till now, the clinical implementation of three techniques have been reported (Lo et al., 2000; Yarnold et al., 2002; Vinici et al., 2002). All techniques use a two-field approach and a relatively simple segmental IMRT technique to optimize the dose distribution (Donovan et al., 2000; Kestin et al., 2000; Lo et al., 2000). Yarnold et al. (2002) reported that the early results of a randomized trial of standard radiotherapy versus IMRT suggest that reduction in unwanted dose inhomogeneity impacts on clinically observable late breast changes.

Position verification

The IMRT technique presented in chapter 2 delivers 88% of the dose with an open field containing the entire breast. The technique is therefore relatively insensitive to organ motion and setup errors and no differences compared to conventional treatment must be taken into account. The same margin was therefore used as conventionally applied for geometric uncertainties. Using a similar segmental IMRT technique as presented in chapter 2, Hector et al. (2000) showed that, although the IMRT treatment was more susceptible to patient movement, it was still superior compared to the standard treatment when considering the dose outside 95-105%. Studying the effect of intrafraction motion for dynamic IMRT, George et al. (2003) found no statistically differences between the planned and expected dose distributions. As reported by Fein et al. (1996) and Lirette et al. (1995) portal images can be used for position verification for breast irradiation. The effect of normal respiratory function was thereby smaller than the effect of interfraction motion. A similar tech-
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nique can be applied for the IMRT technique due to the use of an open field with similar size as conventionally used. Position verification might reduce the margin and therefore reduce the dose to the heart and lung. An improved breast board may also result in better reproducibility of the patient, and reducing the inter-fraction motion. For further improvements of the reproducibility, active breathing control (Wong et al., 1999) could be applied. Beside improving the reproducibility, the separation between the chest wall and the heart is increased during deep inspiration. Sixel et al. (2001) showed that the deep inspiration breath hold technique has the potential to reduce the irradiated heart volume, and could be considered for clinical introduction.

**Target delineation**

For analysis of the breast, the PTV and the lungs were delineated. Lead wires were used to visualize the conventional field borders on the CT scan. In contradiction with the use of the inverse planning software used in chapter 3 and 4, the delineation of the PTV and the lung is not necessary for treatment planning. Using the 2-field IMRT technique presented in chapter 2, only the conventional field borders are required. Therefore, the introduction of the technique will not require extra time for delineation. Using the conventional field borders, many patients have been successfully treated. To achieve a more conformal dose distribution, however, delineation might be useful. Using the MLC, the field can be shaped around the target in order to prevent dose the lung and heart. Inter- and intra-observer variation in the delineation of the breast on CT scans can be rather large (Hurkmans et al., 2001a; Pitkänen et al., 2001). Differences between the breast parenchyma and fatty tissue can be difficult to distinguish. Detailed delineation protocols are therefore necessary for delineation of the breast for clinical practice.

**Extensions to 2-field IMRT**

In literature, the planning studies aim at a homogeneous dose distribution in the whole breast, an extra dose to the tumor bed is thereby not included. A large number of patients, however, receive this extra boost dose. The extra fields used to deliver the boost dose can result in an extra dose to the lung and heart. Integration of the boost in the IMRT technique would therefore be useful. The complexity of the geometry thereby increases and a simple form of dose painting is performed with two dose levels. In order to achieve a conformal dose distribution with two dose levels, the use of extra non-opposing tangential fields is probably unavoidable. This will also result in some extra dose to surrounding normal tissues. It will be difficult to incorporate the boost in the technique presented in chapter 2, because it is based on the equivalent path length and tends to achieve a homogeneous dose distribution. The aim of an integrated boost technique is, however, two level
dose painting. An inverse planning system similar to that used in chapter 3 might be useful. This is, however, currently not possible for clinical practice due to the simple dose model used for inverse planning.

An other extension of the 2-field IMRT technique is the integration in the multiple field techniques used to irradiate the axillary, supraclavicular and internal mammary nodes for breast cancer patients with positive lymph nodes. The technique presented in chapter 2 can be integrated in the multiple field technique used at our department (Lagendijk and Hofman, 1992). It can also be used to improve the match line between the tangential fields and the parasternal field. These conventional fields might, however, also be improved in the future using conformal radiotherapy. The anatomical boundaries of the regional lymph node target volumes should therefore be investigated (Dijkema et al., 2003). Cho et al. (2002) compared different radiotherapy techniques, including IMRT, for the irradiation of the breast and upper mammary nodes. IMRT showed the best target coverage. The lowest NTCP values for heart and lung were found for the IMRT technique and a technique using oblique electron fields. Remouchamps et al. (2003) reported that moderate deep inspiration breath hold significantly reduces heart and lung doses when deep tangential fields are used for locoregional irradiation of the breast. The dose homogeneity was improved using IMRT, while the dose to the heart was slightly reduced.

7.4 Head-and-neck cancer

Segmental IMRT technique for oropharyngeal cancer

A segmental IMRT technique was developed for the irradiation of oropharyngeal cancer. Beside the ability to reduce the dose to the normal tissues, such as brain, spinal cord and parotid gland, and creating highly conformal dose distributions, IMRT was used to apply a simple form of dose painting. The aim was to deliver three different dose levels: one to the CTV of the lymph nodes, one to the CTV of the primary tumor and one to the GTV of the primary tumor. The different dose levels were simultaneously delivered in 30 fractions, resulting in a simultaneous integrated boost strategy (Mohan et al., 2000). Like Mohan et al. (2000), we used an isoeffect relationship based on the linear-quadratic model to design IMRT fractionation strategies. Care should be taken when designing a fractionation strategy when delivering multiple dose levels simultaneously. Low fraction doses result in long treatments. High fraction doses can result in short treatment duration but also in an increased risk of injury to the embedded normal tissue. Until late complications (Withers et al., 1995c; Maciejewski et al., 1989) of the IMRT fractionation strategies are evaluated, care should be taken when escalating the dose. For the clinical introduction we therefore started with an increase of 3
Gy to the GTV.
Due to the complex geometry of the volumes of interest, most groups used an inverse planning algorithm based on dose constraints to volumes of interests to develop an IMRT technique for oropharyngeal cancer. Studying the effect of the use of positioning margins for the parotid gland, Manning et al. (2001) used a dynamic IMRT technique and nine beams for the irradiation of two oropharyngeal tumors. Vineberg et al. (2002) reported that sparing of the parotid glands is possible without compromising target dose homogeneity for irradiation of oropharyngeal cancer. Using nine beams, their optimized fluence profiles were deliverable with either segmental or dynamic IMRT. It was, however, not clear whether the dose was calculated using the deliverable segments or using the optimized fluence. Only Wu et al. (2000) did show data, although not quantitative, that supported the choice of nine beams for the irradiation of three head-and-neck tumors, including an oropharyngeal case. Chao et al. (2000) used tomotherapy-based IMRT for the irradiation of oropharyngeal cancers.

For segmental IMRT, the total number of segments is an important factor, since the treatment time is closely related to the total number of segments. As presented in chapter 3, the dose homogeneity correlated with the total number of segments. For clinical introduction, approximately 100 segments were used. More segments will result in too long treatment times (> 25 min.). The total number of segments is determined by the number of beams and the number of segments per beam. Minimizing the number of beams without reduction of the quality of the treatment would be useful. This might be achieved by applying beam orientation optimization (Pugachev et al., 2001). The saturation level, for dose homogeneity in the target volumes, might than be reached using fewer beams. It could, however, also result in more segments per beam to achieve the same dose homogeneity similar to the findings of chapter 3. Beam optimization might result in better sparing of organs at risk adjacent to the target volumes. Chapter 3 shows that the five-beam plans result in a lower dose to the parotid gland than other beam geometries. Although beam orientation optimization might improve the treatment, it is still hampered by long computing times needed for the optimization process (Pugachev et al., 2001; Rowbottom et al., 2001). Another way to achieve fewer segments is to optimize the sequencing process. Different segmentation methods can result in a different amount of segments (Potter et al., 2002). In chapter 3 and 4 the optimized fluence is divided into equidistant levels. Another division of the optimized fluence might also result in fewer segments. If, for example, the minimum monitor units delivered by one beam is 50 % of the total, this 50 % could be delivered in one segment instead of five in case the fluence is divided in 10 levels. Another method to reduce the number of segments is profile smoothing.
For the dose calculations in chapter 3 and 4 a bixel resolution of 1 cm × 1 cm is used. The use of a higher bixel resolution might improve the dose distribution. For a simple “C”-shaped target volume, Shepard et al. (1999) reported an increase in
dose homogeneity for higher bixel resolution. For the 3D irradiation of the prostate, Kubo et al. (1999) showed more sparing of the rectum and bladder when using a micro-multileaf (1.7-3 mm leaf width) instead of a normal MLC with 10 mm leaf width. Beside the ability to improve the blocking of the surrounding normal tissue using a higher resolution, it might be easier to deliver a heterogeneous dose distribution using a higher resolution. A higher resolution can result in a better sampling of the target volume, resulting in more degrees of freedom to deliver a dose to an individual part of the target volume. In the direction of the leaf motion, the resolution can be easily adjusted by choosing a smaller leaf step size, in the opposite direction the resolution is limited by the leaf width. In order to achieve a higher spatial resolution micro-multileaf collimators have been constructed, with leaf widths projecting in the isocenter between 1.6 and 4.5 mm (Cosgrove et al., 1999; Schlegel et al., 1992). The disadvantage of these systems is the limited field size. Other attempts to increase the resolution are the use of two superimposing MLC fields with a small shift in isocenter (Galvin et al., 1996) or a collimator rotation (Evans and Partridge, 2000; Otto and Clark, 2002; Alfredo and Siochi, 2000). Topolnjak et al. (2003) reported a design study for a six-bank multi-leaf collimator, which has a resolution comparable to the micro-multileaf collimators and a field size of at least 40 cm. Bortfeld et al. (2000) utilized the methods of sampling theory and the theory of linear systems in an effort to identify the optimum leaf width. For a 6-MV beam this resulted in a minimum leaf width of 1.5-1.8 mm. Although a high resolution of the fluence matrix may have some advantages, the disadvantage for segmental IMRT is that it can result in more segments.

Parotid gland

The parotid glands are located adjacent to the lymph node containing target volume. Therefore it is rather difficult to avoid irradiation to the parotid glands, without reduction of the TCP. To achieve the prescribed dose in the lymph nodes, a dose gradient outside the PTV, thus partially in the parotid glands, is necessary to allow dose build up. Reduction of parotid dose could result in lower dose regions in the lymph node containing region (chapter 4), i.e. moving the dose gradient into the lymph node containing region. It should be investigated whether these lower dose regions result in an increased risk regarding local failure. Furthermore, the margin taken into account for position verification will result in an increased dose to the parotid gland (chapter 4). Dose reduction can therefore also be achieved by accurate position verification. Using the data of the marker based position verification (chapter 5) as input for the recipe of Van Herk et al. (2000), a margin of approximately 3 mm is determined. When decreasing the margin from 6 mm to 3 mm for moderate sparing of the parotid glands, the mean dose to the parotid gland reduces by approximately 4 Gy corresponding with a decrease in NTCP for xerostomia from 44 % to 35 %. 
In order to decrease the dose to the contralateral parotid gland, the cranial border to which the contralateral lateral lymph nodes are irradiated might be lowered (Eisbruch et al., 1998). In a recent study of Braam et al. (2003), it was shown that for a group of N+ patients metastasis of oropharyngeal cancer rarely appears high cranially on the contralateral side, indicating that the probability for microscopic metastasis in that area in N0 patients must be small. Lowering the cranial border of the lymph node containing area from C1 to C2 level II results in a decrease in mean dose to the parotid gland of approximately 6 Gy (Astreinidou et al., 2003). The NTCP did thereby decrease by approximately 12%. These results are currently clinically used.

Delineation of volumes

In order to deliver highly conformal dose distributions with different dose levels, accurate delineation of all volumes involved is necessary. Recent articles have reviewed the normal anatomy of the neck (Wijers et al., 1999; Nowak et al., 1999; Gregoire et al., 2000). These were mainly focused at the delineation of the lymph node regions or levels in the normal neck. Guidelines are provided for the delineation of the electively treated lymph nodes. For the target volumes, the delineation relies on historical information from surgical pathologic experiences. Few studies reported the delineation of oropharyngeal tumors. In a study of Nishioka et al. (2002) was reported that image fusion between 18FDG-PET and CT/MRI was useful in GTV and CTV determination for oropharyngeal cancer. Rasch et al. (1997) reported that MRI-derived GTVs were smaller and had less interobserver variation than the CT-derived GTVs for advanced head-and-neck cancer. A pilot study is started at our department to investigate the use of PET for target delineation of head-and-neck tumors. Beside the target volumes, also organs at risk should be accurately delineated. The delineation of the brain and the spinal cord is relatively easy, because these organs are enclosed by bony structures. The parotid glands is delineated on CT scans, the use of MRI might be more accurate due to the ability of imaging soft tissues. There are however no delineation studies concerning these normal tissues.

Position verification

Due to the complex geometry and high fraction doses, accurate position verification is essential for head-and-neck tumors. High doses should be delivered to the targets, while the dose to the brain and spinal cord should be minimized. A low dose to the parotid gland is also important to improve the quality of life after radiotherapy. As shown in chapter 4 one way to achieve this aim is accurate patient positioning. Position verification of head-and-neck tumors is usually performed by
applying an EPID or a megavoltage film (Hurkmans et al., 2001b). The position of bony structures is thereby measured relative to a reference position. In a review of Hurkmans et al. (2001b), a standard deviation of the systematic error of 1.6-4.6 mm and a random error of 1.1-2.5 mm (1 standard deviation) was reported for the head-and-neck region. In chapter 5 markers were used for position verification purposes. Markers are more easy to detect compared with bony structures, and the determination of the coordinates is straightforward. Regarding IMRT, marker-based positioning verification is especially useful due to the small fields used for segmental IMRT with non-conventional gantry angles. When the marker is implanted inside a relatively mobile organ like the prostate (Dehnad et al., 2003), it can be used to remove the systematic errors, while using bony structures this is not possible.

Beside interfraction motions, intrafraction motions should be evaluated since these can contribute to the margins taken for setup uncertainties. In the head-and-neck region, intrafraction motion can be caused by organ motions, such as swallowing, breathing, or tongue motions (chapter 6). Due to the low incidence, swallowing has a minor influence on the dose distribution (chapter 6). Most organs in the head-and-neck region are, however, relatively immobile and attached to bony structures. Intrafraction motion may also occur due to patient movements or relaxation of the muscles. This might become an issue for IMRT treatments with long treatment times and result in an unstable position relative to the start of the irradiation. The delivery of an IMRT treatment plan can take 20 minutes. Markers could be used to quantify the intrafraction motion, by taking multiple images during a single fraction. When the determined intrafraction motions are large during long treatments, it could be investigated whether marker-based position verification should be applied during the treatment. This could reduce the margin taken for geometric uncertainties.

### 7.5 Conclusion

Two different segmental IMRT techniques have been developed in this thesis for respectively irradiation of the breast and the oropharynx. Both techniques have been implemented clinically. Various other improvements can be applied as have been discussed in this chapter. Part of them, concerning position verification for head-and-neck cancer, have been investigated in this thesis.