Designing IMRT for lung cancer
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Chapter 1

General introduction
Chapter 1

1 Dose escalation of lung cancer treatment

Non-small cell lung cancer (NSCLC) is a common tumour with a poor prognosis because a large proportion of the patients is inoperable at the time of diagnosis. Approximately 40% of the patients presenting with NSCLC is inoperable because of distant metastases, another 40% because of the spread of the regional disease for which radiation therapy is the principal mode of treatment. Radiation treatment plans of patients treated for NSCLC have a poor outcome with median survival times of the patients of 8 to 10 months, 2-year survival of about 10 to 20%, and 5-year survival of only 3 to 7% [55,56,62]. Patterns of failure analysis indicates that both persistent or recurrent intra-thoracic disease and distant metastases contribute to this poor outcome. In a study by Amagada et al. [2] in which tumour control was evaluated based on routine bronchoscopy during follow up, local disease eradication was achieved in only 17% of patients examined one year after irradiation. Better control of the loco-regional disease seems important for several reasons. Firstly, loco-regional disease is often the direct cause of death due to mechanical effects within the lung and mediastinum. Secondly, locally persistent or recurrent thoracic disease can serve as a focus for metastatic dissemination. Thirdly, if more effective systemic therapy becomes available that might function in an adjuvant manner, thoracic disease eradication becomes a necessity.

From RTOG 73-01 (randomisation to a split course of 40 Gy, or a continuous fractionation schedule of 40-60 Gy), it was concluded that a higher dose of radiation yielded a greater proportion of complete responses, resulting in higher intra-thoracic tumour control [55,56]. Increased survival was noted in patients with complete tumour responses. Relapses in the thorax resulted in a death rate similar to the death rate of patients who developed distant metastases. In RTOG 83-11 (hyperfractionation to 60-79.2 Gy), patients were randomised to a minimal total dose varying between 60 and 79 Gy. Fractions of 1.2 Gy were administered twice daily. Favourable patients showed an improved survival following 70 Gy compared with lower doses [12]. However, no improvement was seen with doses above 70 Gy. A possible explanation might have been the treatment delays that were more common in the higher dose groups, and on reanalysis it was shown that treatment delays were associated with decreased survival [13]. In RTOG 88-08 standard radiotherapy (60 Gy) was compared with the same treatment combined with induction chemotherapy and hyper-fractionated radiotherapy to a higher dose (70 Gy). Survival was improved at 3 years for the high dose group [61].

From the results of these RTOG trials Byhardt [10] concluded that the evidence is fairly good that total doses higher than the standard 60 Gy are associated with improved local tumour control. For that reason a new Phase I/II RTOG trial, i.e. RTOG 93-11, was started which will evaluate the use of 3D conformal treatment techniques. Preliminary results of prospective trials using high-dose 3D conformal radiotherapy of NSCLC are promising but the incidence of pneumonitis demands careful selection of patients and irradiation techniques for future dose escalation [1,28,31,68]. Other recent clinical trials for patients with NSCLC have also demonstrated that treatment intensification of radiotherapy leads to a better survival
in this patient group and therefore provides extra evidence that dose escalation may lead to a better local control and survival. This is for example shown in the EORTC trial where the addition of daily Cisplatin leads to improved local control and survival, but no reduction of the rate of distant metastases was observed [62]. Similarly, the CHART trial revealed improved survival by reducing the overall treatment time of the irradiation period from 6 weeks to 12 days [60] once again showing a beneficial impact of intensification of the irradiation of the loco-regional tumour. Martel et al. suggest that for NSCLC-patients, the dose to achieve significant probability of tumour control (> 50 %) may be on the order of 84 Gy for local progression-free survival of more than 30 months [48]. Hayman et al. [30] have shown that dose escalation in the lung can be safely applied using three-dimensional conformal treatment planning and segregating patients by the volume of normal tissue irradiated.

At The Netherlands Cancer Institute (NKI/AvL), a phase I/II dose escalation study is ongoing for non-small cell lung cancer patients. Patients have histologically proven NSCLC with stages IIIA or IIIB (N3 excluded). Treatment plans are applied that conform the planned 95 % isodose level to the planning target volume (PTV), which is a 15 mm 3-D expansion of the gross tumour volume (GTV) as delineated on a CT-scan. The risk of radiation pneumonitis is assessed before treatment by calculating the mean normalised total dose (NTDmean) of the lungs from the individual 3-D treatment plan. Four separate patient groups are formed each with an increasing risk of radiation pneumonitis. For each group, the prescribed dose is escalated in steps of 6.75 Gy (3 fractions of 2.25 Gy). However, the initial dose level is different for each group and depends on the estimated relative risk of developing radiation pneumonitis. The overall treatment time may not exceed 6 weeks.

2 Clinical factors impeding dose escalation

The dose in normal tissues like the oesophagus, spinal cord, heart and lungs, is a complicating factor in radiation treatment of lung cancer. This means that any approach of dose escalation is limited by toxicity of these organs at risk (OAR).

Tolerance data of the oesophagus are scarce. Burman et al. [9] and Emami et al. [24] reported in humans a TD50 (end-point: clinical stricture or perforation) of 68 Gy and 70 Gy respectively, with a small volume effect. In studies on lung cancer, clinical stricture or perforation was not observed in the consecutive RTOG trials [10] nor in the studies using high-dose conformal radiotherapy [28,31,68]. The Burman et al. and Emami et al. TD50 data might therefore be overestimating the radiation sensitivity of the non-diseased oesophagus. Although late oesophageal toxicity is common following high-dose conformal radiotherapy, it is rarely severe [44].

Most of the reported cases on myelopathy are due to the large dose per fraction which was commonly used during the 1970s [63]. The effect of fractionation is large in the sense that the tolerance rapidly decreases with fraction sizes above 2 Gy. It is believed that the dose leading to a 50 % probability of complications, TD50, is
between 70 and 80 Gy [24], for 2 Gy or 2.2 Gy fractions [64] with myelopathy as the endpoint. No volume effect has been detected for the spinal cord [45,63]. A dose of 50 Gy is generally believed to give a complication rate less than 1% [45,50,74].

Based on clinical data, Emami et al. [24] cite a TD50 of 50 Gy for the whole heart (end-point pericarditis). However, patients with irresectable disease have a poor prognosis with a 5-year survival of not more than 5% [22].

The most important dose limiting organ for treatment of lung cancer, however, is the lung itself. Based on clinical data, Emami et al. [24] cite a TD50 (end-point radiation pneumonitis) of 24.5 Gy for the whole lung and a large volume effect (Burman et al. [9]). These figures are based on data in which the effect of tissue inhomogeneities on the dose calculation is not taken into account. A number of authors compared observed incidence of pulmonary complications with calculated NTCPs. For mantle field irradiation a good correlation was found between calculated NTCPs and observed incidence of pneumonitis (Martel et al. [49]). For lung cancer patients the correlation is weak [27,49]. In this case, the data suggest that the parameters used in the model of Burman et al. should be modified to get a better fit. Oetzel et al. [53] found, however, a good correlation between the estimation and incidence of radiation pneumonitis for lung cancer irradiation. Several groups used SPECT to determine a local dose-effect relation for reduction of perfusion in the lung [4,5,15,46,65,71,72]. Boersma et al. [5] calculated an "Overall Response Parameter" (ORP), which is the mean reduction in perfusion over the total lung. They observed a strong correlation between the ORP and the reduction in overall lung function parameters (e.g., vital capacity). They also observed a correlation between the ORP and the incidence of radiation pneumonitis in these patients. However, the limited number of patients and the low incidence of pneumonitis did not allow a reliable comparison with existing models for the normal tissue complication probability (NTCP) [14]. The tolerance of the lung strongly depends on the irradiated volume [24]. Both the volume of lung tissue receiving a dose of more than 20 Gy (V20) [27], and the mean lung dose (MLD) [40] can be used as an estimator for the NTCP of the lungs.

In the previously mentioned phase I/II dose escalation study, an absolute dose constraint of 50 Gy is set for the spinal cord. For the oesophagus an effective volume constraint is set [39], with a value of 30% at 80 Gy. For the heart three points in the cumulative dose volume histogram are defined: The cumulative DVH should be below the following points: 100 volume % of the heart at a dose level of 40 Gy, 66% at 50 Gy and 33% at 66 Gy. The mean lung dose is used as an estimator for the NTCP of the lungs and should be minimised during treatment planning.

3 Technical difficulties in irradiating lung tumours

Before going into the technical difficulties, current clinical practice in the irradiation of lung cancer with curative intent has to be elucidated. The goal of
treatment planning, according to the recommendations of the ICRU [34,35], is to conform the 95 % isodose level to the planning target volume (PTV) while limiting the maximum dose to 107 %, i.e., a homogeneous dose distribution in the PTV is pursued. The PTV is a geometrical concept. It is constructed from the gross tumour volume (GTV) as delineated by a radiation oncologist on a CT-scan in combination with other diagnostic information. First, the GTV is expanded in 3-D to account for the spread of subclinical disease, yielding the clinical target volume (CTV). The CTV should encompass all clonogenic cells of the primary tumour, involved lymph nodes and metastases. The necessary margin may be up to 8 mm for lung tumours [26]. The CTV is expanded in 3-D into a PTV to account for target delineation errors and tumour movement, e.g., due to set-up errors and patient breathing. Generally the PTV is defined in such a way that the CTV is fully located inside this PTV for (almost) the entire course of a radiation treatment, thus ensuring that all parts of the CTV, and therefore all clonogenic tumour cells, receive at least 95 % of the dose prescribed to the PTV.

3.1 Broadening of the beam fringe

The irradiation of lung tumours is more complicated compared with treatment of tumours at other sites. The attenuation of high energy photons per unit length is lower in low-density tissue compared with unit-density tissue. Furthermore, the increase in the range of secondary electrons in low-density lung tissue (density ± 0.25 g/cm³) with respect to soft-tissue results in a broadening of the beam penumbra [23,33,51,66]. In Figure 1, dose profiles of a 10x10 cm² 8 MV photon field measured at a depth of 10 cm are plotted for both a phantom consisting entirely of water (density of 1.0 g/cm³) and for a phantom consisting of cork (0.25 g/cm³) with a 2 cm build-up layer of water equivalent material.

Figure 1: Dose profiles in water (1 g/cm³) and lung (0.25 g/cm³) density.
Chapter 1

It is clear that both the penumbra width (distance between 20% and 80% of the central axis dose value) and beam fringe width (distance between 50% and 90% of the central axis dose value) increase in low-density tissue like the lung with respect to soft tissue. Also the distance between the 50% isodose level, which corresponds with the field edge, and the 95% isodose level, increases. This means that a larger margin between the field edge and the edge of the PTV is necessary in order to conform the 95% isodose level to this PTV. The difference between both profiles as shown in Figure 1, increases with nominal beam energy. The inward shift of the 95% isodose level may be as large as 15 mm for an 18 MV beam.

Most of the ‘older’ commercially available treatment planning systems (TPSs) apply dose calculation algorithms that do not accurately take into account the effects of low-density tissue on the dose distribution in the patient. If the increased range of secondary electrons and the decrease in photon attenuation is not adequately taken into account, this may lead to an incorrect calculation of monitor units as well as an incorrect choice of field sizes and field shapes. This may result in a too low dose to (outer parts of) the target volume. Moreover, older TPSs often assume electron equilibrium at the centre of the target volume where monitor units (MUs) are calculated. For small field sizes (< 5 cm2), however, the increased range of the electrons can lead to a lack of electron equilibrium on the central beam axis, which may introduce an additional error in the MU calculation. The use of simple dose calculation algorithms will also lead to an inaccurate calculation of the dose in healthy lung. Accurate calculation of this dose is important because the lung is often the dose limiting organ during treatment of lung cancer.

3.2 Patient breathing

Irradiation of lung cancer is at present mostly done with the patient breathing freely. As a consequence, the target volume and surrounding tissue are moving with the breathing cycle. This movement must be taken into account in the treatment planning process. Two aspects are of importance: 1) use of a representative CT-scan for treatment planning; 2) incorporation of target movement in the design of beam portals. Balter et al. [3] showed that a CT-scan, made with the patient breathing freely, may introduce a significant uncertainty in size and position of organs at risk, especially near the diaphragm. For lung cancer, a significant reduction in calculated NTCP of the lung was seen when comparing treatment plans based on CT data made during maximum exhalation and plans based on CT data gathered during maximum inhalation. Ross et al. [59], using ultra fast CT, observed tumour movement as a consequence of both cardiac and respiratory activity. Tumours moved an average 6.1 mm laterally and 2.7 mm antero-posteriorly. Lateral movement was greatest for tumours located adjacent to the heart or aorta and cranial-caudal movement was greatest for tumours near the diaphragm. Minimal movement was observed in lesions in the upper lobe and those attached to the chest wall. In an in-house study tumour motion during one treatment was studied for ten patients using a fast portal imaging device [internal communication]. The results are shown in Table 1.
Table 1: Tumour motion during irradiation in lung cancer patients (maximum displacement in mm)

<table>
<thead>
<tr>
<th></th>
<th>Cranial-caudal (mm)</th>
<th>Lateral (mm)</th>
<th>Anterior-posterior (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper lobe</td>
<td>2-6</td>
<td>1-5</td>
<td>1-3</td>
</tr>
<tr>
<td>Middle and lower lobe</td>
<td>5-8</td>
<td>3-9</td>
<td>2-3</td>
</tr>
</tbody>
</table>

The consequence of respiration is that a larger margin around the CTV has to be used than to account for beam fringe and set-up errors alone. Consequently, a larger volume of lung and other organs at risk will be irradiated during irradiation of middle and lower lobe tumours compared with tumours in the upper lobe.

3.3 Set-up errors

Besides patient breathing, random and systematic (set-up) errors also necessitate the use of a (increased) margin between CTV and PTV. At The Netherlands Cancer Institute portal imaging is performed routinely using an electronic portal imaging device (EPID). Valuable insight into the magnitude of set-up errors, both random and systematic, has thus been obtained (Table 2). A set-up correction protocol is used in order to minimize systematic set-up errors. Such a reduction in set-up errors allows a smaller margin between CTV and PTV.

Table 2: Standard deviations for the systematic and random set-up errors for a group of 38 lung cancer patients for which a set-up correction protocol is applied. Also given are the data with the corrections removed.

<table>
<thead>
<tr>
<th></th>
<th>Corrections included</th>
<th>Corrections removed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left-right</td>
<td>Cranial-caudal</td>
</tr>
<tr>
<td>Systematic error</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Random error</td>
<td>3.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

3.4 Location of the tumour

Besides the aforementioned technical difficulties in irradiating lung tumours, a further characteristic that makes irradiation of lung cancer more complicated compared with other cancer sites, is that the target region is surrounded for a large part by an organ at risk, i.e., the lung. Therefore, only a moderate reduction of the dose in this OAR is possible by a smart choice of directions of beam incidence, e.g.
by using non-coplanar beams. Any reduction in lung dose should therefore be obtained by reducing field sizes, whether or not in combination with beam intensity modulation.

4 Current status of treatment planning of lung cancer

4.1 Conformal treatment plans

The most simple way of treating lung cancer is the use of non-conformal beam set-ups. Nowadays this is often used for treatments with a palliative intent. Field shapes and monitor units are determined without using a sophisticated treatment planning system. In this thesis, however, we will not discuss this type of irradiation and we will limit ourselves to the irradiation of lung tumours with a curative intent.

Employing conformal beams, either by using customized blocks or a multileaf collimator (MLC), the 95 % isodose surface can be tailored close to the planning target volume. The accompanying NTCP of the lung is, however, large because of the broad beam fringe in low-density lung tissue. The aim of improved treatment planning of lung cancer is therefore to reduce the volume of irradiated healthy lung tissue, while keeping the coverage of the target volume, i.e. the PTV, optimal. Armstrong et al. [1] compared conventional with conformal treatment planning and found that 3-D conformal treatment planning leads to better target coverage and to substantial reduction in NTCP of the lung, oesophagus and spinal cord. Graham et al. [27] compared several types of conformal plans, having an increasing level of complexity, and found that escalation of tumour dose without increasing the NTCP of normal tissue is only possible when complex plans, using a non-coplanar beam set-up, are used. Marks et al. [46,47] used pre-treatment SPECT perfusion scans to locate areas of inhibited lung function due to the presence of the tumour. Based on these data, beam portals are designed to minimize irradiation of functioning lung tissue.

4.2 Intensity modulation for further improvement

Variation of the photon fluence over the area of each treatment field can lead to a considerable improvement towards the desired dose distribution, i.e. a high dose in the target region and a low dose in organs at risk [e.g. 7,20,21,52,66]. Beam modifiers have been applied for this purpose for a long time, but, apart from standard wedges, the routine use of tissue compensators or transmission blocks in the clinic has remained limited. The main reason for this limited clinical implementation was the considerable effort required for the reliable design, production and quality control of these mechanical devices as well as the time necessary at the treatment machine for their daily insertion. Movement of the leaves of an MLC during radiation is, at least in principle, a more feasible approach for the routine clinical application of beam intensity modulation [6,36,42,77]. An alternative method is tomotherapy, where an intensity profile is generated by positioning vanes
in a long thin slit oriented transaxial to the patient, in combination with couch translation [43].

Two different approaches for the clinical use of intensity modulated radiotherapy (IMRT) have been described and implemented: dynamic versus segmented IMRT. Dynamic IMRT-treatments can approximate almost any dose distribution by mathematical transformation of the required intensity profiles into a prescription for the movement of the leaves [e.g. 11,70,73]. In segmented IMRT, also called 'step-and-shoot', the requested intensity profile is approximated by a limited number of fixed beam segments. As an example of segmented IMRT, De Neve and colleagues have shown that an IMRT-technique with a limited number of beam portals and segments (< 20) is sufficient to obtain an improved dose distribution for most head-and-neck treatments [17]. The approach of segmented IMRT has the advantage of being simpler, both in the treatment planning stage and during dose verification, because the treatment plan can be considered to exist of a manageable number of conventional treatment 'fields'. It can therefore be considered as a 'natural' extension of existing treatment techniques. This approach is, however, not yet routinely used to irradiate lung cancer patients.

A number of treatment planning studies have shown that a large gain in the irradiation of several cancer sites is possible by means of intensity modulated radiotherapy [32,57,58,69,76]. The gain is either expressed as an improvement in dose distribution over the target volume or in a reduced probability of complications of organs at risk. IMRT is already routinely used for irradiating patients with cancer at several sites, such as the breast, the prostate and the head-and-neck region [8,16,25,42]. For lung tumours however, only a limited number of studies are available showing the benefit of IMRT. This despite the fact that the broad beam fringe in low-density lung tissue makes lung cancer such an excellent tumour site for the use of intensity modulation. The beam fringe can be substantially sharpened using relatively simple intensity modulation, allowing a large reduction in field sizes and sparing of organs at risk. A factor that may play a role is that dose calculations performed by commercial treatment planning systems for lung cancer treatments were not very accurate until a few years back. Present-day convolution algorithms and Monte Carlo methods allow accurate calculation of dose distributions in inhomogeneous surroundings. Use of either approach in an (automatic) optimisation routine for IMRT, however, still requires prohibitively long calculation times.

Derycke and colleagues showed, by means of a planning study, that IMRT is advantageous for the irradiation of lung cancer [18,19]. Their class solutions are, however, not yet used clinically. One of the reasons might be the limitations of the dose calculation algorithm. Brugmans et al. [7] showed by means of a dosimetric study that a relatively simple approach of IMRT, i.e. use of only a single segment near the beam edge, is beneficial for the optimisation of the dose distribution during lung cancer treatments. The extra segment near the beam edge leads to a steeper dose gradient, which allows shrinking of field sizes while maintaining dose homogeneity in the target structure (i.e. the PTV). The reduction in field sizes leads to sparing of lung tissue and therefore allows dose escalation. Dirkx et al. [20,21]
have implemented the approach of extra segments near the beam edge into clinical practice for their coplanar treatment technique. For practical reasons they only apply extra segments at the cranial and caudal beam edge of one beam, but this additional dose already allows a considerable reduction in field sizes and dose in the lungs while dose homogeneity in the target volume (PTV) is maintained.

5 Reduction of margin between CTV and PTV

The use of IMRT to sharpen the beam fringe and to conform the high dose region more closely to the PTV is not the only method to improve the irradiation of lung tumours. Reduction of field sizes and therewith sparing of the lungs and other organs at risk can also be achieved if the margin from CTV to PTV can be reduced.

It is suggested that if the breathing motion of the CTV is effectively eliminated by respiration-gated radiotherapy, this margin can be reduced thus enabling the delivery of a higher dose in the CTV without increasing deleterious complications. Two approaches for respiration-gated radiotherapy have been proposed: using breath-hold during inhalation or gating the accelerator at the optimal point in a respiration cycle where tumour movement is minimal [29,37,38,54,67,75].

Another approach to account for respiration-induced tumour motion is by modifying the intensity profiles of incident beams. An increase in the intensity of a beam towards the border of the CTV, combined with a smaller than conventional margin width which incorporates the whole movement of the CTV, can be beneficial. Lind et al. [41] have shown that overcompensation of the dose near the field edge can be used to counter the effects of random errors. Such an approach might, however, also be useful to minimize the effects of respiration-induced tumour motion.

Furthermore, as mentioned previously, a set-up correction protocol can be used to minimize systematic set-up errors and allow a reduction in margin between CTV and PTV.

6 Purpose of the study

Only a few groups have investigated the possible benefit of IMRT for the treatment of lung cancer. Even less groups are actually using IMRT-techniques for lung cancer treatment in routine clinical practice. Nevertheless the lung is an excellent tumour site for the use of intensity modulation because of the broad beam fringe in low-density tissue that can be easily compensated, thus allowing dose escalation. An important reason for this lack of effort may be that accurate dose-calculation algorithms that require clinically acceptable calculation times have only recently become available.
In the on-going phase I/II dose escalation study, the mean lung dose, which is used as an estimator for the probability of radiation pneumonitis, is a limiting parameter for the prescribed dose. Treatment plans are applied that conform the planned 95% isodose level to the PTV, which is a 15 mm 3-D expansion of the GTV. Current protocol guidelines require that dose homogeneity in the PTV should be maintained for conformal treatment plans. As a consequence, escalation of the prescribed dose will be limited because at higher dose levels an unacceptable high probability of lung complications will occur, thus limiting the probability of tumour control. A research project has therefore been started in our institution to investigate whether the use of IMRT might be beneficial to increase the probability of tumour control while limiting the complication probability of the lungs and other organs at risk.

When we started with this project, two factors had to be taken into account. First, the current clinically applied treatment plans of the dose escalation study are designed using a simple inhomogeneity correction algorithm that does not accurately take into account the effects of low-density lung tissue on the dose distribution. Knowledge of the accuracy of this algorithm and its effect on clinically applied treatment plans is essential when designing conformal treatment plans and even more so when applying intensity modulation. Second, data were available at for systematic set-up errors, random set-up errors and respiration-induced tumour motion for NSCLC-patients. Each of these tumour motion parameters has a different effect on the dose distribution over the clinical target volume and on the design of the optimum intensity modulated treatment plan. Therefore, the purpose of our study is to pave the way from 'classical' conformal radiotherapy on a static volume (PTV) to intensity modulated radiotherapy of a moving CTV to allow further dose escalation of NSCLC-patient treatments, taking into account tumour motion parameters.

7 Outline of this thesis

First, the accuracy of our current clinically applied dose-calculation algorithm was determined using film and ionisation chamber measurements in a specially developed phantom simulating a tumour located centrally in a lung (Chapter 2). Using the same phantom and a choice of field sizes based on the same algorithm, an upper limit was determined for the effects of tumour motion parameters on the probability of tumour control by means of a worst case scenario (Chapter 3). Furthermore, this study provided information on the relation between the planned dose distribution and the actually delivered dose distribution for our current clinically used treatment plans.

With the mean lung dose as an estimator for the NTCP of the lung, we assessed whether the probability of tumour control of lung tumours might be increased by dose escalation in combination with a reduction of field sizes and accepting an increased target dose inhomogeneity while maintaining a constant MLD (Chapter
4) The feasibility of such an approach of dose escalation under constraint of a constant MLD was first tested using a numerical simulation and later employed on a NSCLC-patient. Furthermore the achievable gain in probability of lung tumour control using intensity modulation under the same constraint was investigated (Chapter 5). In addition, the benefit of incorporating SPECT lung perfusion data in the treatment planning process has been determined (Chapter 6).

In Chapter 7 we will discuss the results obtained in our study, the prospects of applying IMRT for lung cancer treatments and ideas for some future investigations.

References


Chapter 1


