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Target volume determination in radiotherapy for non-small-cell lung cancer – facts and questions

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Although the precise target volume definition in conformal radiotherapy is required by ICRU Report 50 and 62, this task in radiotherapy for non-small-cell lung cancer (NSCLC) is often controversial and strict accordance with ICRU requirements is hard to achieve. The Gross Tumour Volume (GTV) definition depends mainly on the imaging method used. We discuss the use of new imaging modalities, like PET, in GTV definition. The Clinical Target Volume (CTV) definition remains a separate, and still unresolved problem, especially in the part concerning the Elective Nodal Irradiation (ENI). Nowadays, there is no unified attitude among radiation oncologists regarding the necessity and extent of ENI. The common use of combined treatment modalities and the tendency to dose escalation, both increasing the potential toxicity, result in the more frequent use of involved-fields techniques. Problems relating to margins during Planning Target Volume (PTV) of lung cancer irradiation are also discussed. Another issue is the Interclinician variability in target volumes definition, especially when there is data indicating that the GTV, as defined by 3 D-treatment planning in NSCLC radiotherapy, may be highly prognostic for survival. We postulate that special attention should be paid to detailed precision of target volume determination in departmental and trial protocols. Careful analysis of patterns of failures from ongoing protocols will enable us to formulate the guidelines for target volume definition in radiotherapy for lung cancer.

Wyznaczanie obszarów do napromieniania w radioterapii niedrobnokomórkowego raka płuca

Dokładne określenie obszarów do napromieniania, zgodnie z wymaganiami ICRU (International Commission on Radiation Units and Measurements), jest obecnie jednym z kryteriów poprawności stosowania radioterapii konformalnej. Spełnienie kryteriów ICRU, odnośnie definiowania poszczególnych obszarów do napromieniania (GTV, CTV, PTV), napotyka w radioterapii niedrobnokomórkowego raka płuca na szczególne trudności. Znane są duże różnice w określaniu makroskopowej objętości guza (GTV) pomiędzy lekarzami, nawet w obrębie jednego ośrodka. Wiąże się to z trudnością w interpretacji danych radiologicznych w przypadku raka płuca, brakiem protokołów i szczegółowych instrukcji, dotyczących tego zagadnienia, a także stosowaniem różnych technik diagnostycznych. Zależność wielkości GTV od stosowanych technik obrazowania, w szczególności zalety i ograniczenia pozytronowej tomografii emisyjnej (PET), są dyskutowane w artykule. Osobny i nierozwiązany problem w radioterapii raka płuca stanowi definicja klinicznej objętości tarczowej (CTV). W artykule omówiono fakty i pytania dotyczące określania CTV jako mikroskopowego szerzenia się choroby w bezpośrednim sąsiedztwie GTV, a także aspekty związane z CTV, określanym jako obszar elektywnego napromieniania (OEN) węzłów chłonnych śródpiersia. Obecnie OEN stanowi temat badań klinicznych. W dobie powszechnego stosowania chemio-radioterapii i eskalacji dawki promieniowania, a także skracania czasu leczenia, istnieje tendencja do zmniejszania obszaru napromieniania. Toksyczność związana z napromienianiem elektywnym, w świetle wielu doniesień, prowadzi do obniżenia zysku terapeutycznego w radioterapii raka płuca. Dyskutowane są problemy związane z ustalaniem wielkości marginesów, celem utworzenia Planowanej Objętości Tarczowej (PTV). Wobec wielu kontrowersji związanych z definiowaniem obszarów do napromieniania w radioterapii raka płuca, przy jednoczesnych doniesieniach, że GTV jest czynnikiem prognostycznym, należy bardzo szczegółowo definiować objętości do napromieniania w protokołach poszczególnych ośrodków. Istnieją doniesienia, że wprowadzenie ścisłych protokołów, związanych z definiowaniem obszarów do napromieniania, prowadzi do znacznego zmniejszenia różnic w zakresie „wrysowywania" objętości przez poszczególnych lekarzy, a tym samym poprawy jakości leczenia. Niejasności związane z tym tematem powinny być oceniane w ramach badań klinicznych.

Key words: target volume, non-small-cell lung cancer, radiotherapy
Słowa kluczowe: obszary napromieniania, rak niedrobnokomórkowy płuca, radioterapia

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Introduction

Conformal radiotherapy should follow ICRU 50 and ICRU 62 criteria concerning target volume definition [1, 2]. In spite of the wide use of conformal techniques, target volume definition remains a controversial issue in radiotherapy for non-small-cell lung cancer (NSCLC). There is no unanimous opinion among radiation oncologists regarding target's delineation in NSCLC radiotherapy. The delineation of the Gross Tumour Volume (GTV) varies between physicians and depends on the type of imaging used. The Clinical Target Volume (CTV) definition is mainly methodology-dependent and is grossly based on institutional opinions regarding the necessity and extent of elective nodal irradiation (ENI). Microscopic tumour extension around the GTV as a part of the CTV isalso not precisely quantified and remains a subject of study. Taking into account physiologic organs motions and set-up inaccuracies, the Planning Target Volume (PTV) is an especially important issue in NSCLC radiotherapy. There are many methodological and technological concepts dealing with the problem of margin reduction for the PTV creation in view of decreasing treatment toxicity.

The major source of uncertainty in determination of the all three volumes is interclinician variability, which could be related either to the lack of respect of protocols or to the lack of a protocol in itself [3, 4]. There exists data indicating that the implementation of departmental protocols can reduce this source of errors. It is advocated to create and consistently follow detailed departmental protocols for target contouring [3].

The current state of art and controversies regarding all three target volumes definitions in radiotherapy for NSCLC are presented below.

Gross Tumour Volume (GTV) definition

The GTV according to ICRU Report 50 criteria is defined as "the gross demonstrable extent and location of the malignant growth" [1]. In case of radical radiotherapy for NSCLC the GTV is related to the primary tumour and mediastinal lymph nodes considered as metastatic.

The size of GTV, as determined in conformal radiotherapy, appears as a highly prognostic factor for survival and local tumour control [5]. It may be important for the stratification of patients for future prospective studies. Therefore special attention should be paid by radiation oncologists in view of the unification of the guidelines concerning GTV determination.

Evaluation of the extent of GTV is based mainly on computed tomography (CT) images, supported by bronchoscopic findings. The use of CT has radically improved the possibility of evaluation of the mediastinal extent of the disease. In the pre-CT era there were no reliable means, besides surgery, to evaluate gross tumour extension in the mediastinum. The inclusion of mediastinal nodes in the irradiation field depended mostly on clinical assumptions of the probability of nodal invasion. In case of adenocarcinoma or squamous carcinoma no systematic inclusion in the irradiation field of the mediastinal area was recommended. For undifferentiated and small-cell lung cancers the lymph node drainage areas within the thorax were irradiated [6]. Although CT remains the most common tool for the definition of the "nodal GTV", its sensitivity and specificity is evaluated to be about 65% [7-9]. Taking into account the limits of CT in evaluation of the "nodal GTV", positron emission tomography (PET) is implemented. The current practice in radiation treatment planning is to consider lymph nodes to be positive, if their dimension is 1 cm or greater in the short axis and include them in the GTV [8, 10]. It seems to be a reasonable clinical compromise, due to the current low availability of the PET. The GTV within mediastinum is contoured using the mediastinal window setting. Evaluation of the "primary GTV" by CT seems quite good, under the condition of keeping the slice thickness to its minimum through the presumed area of the GTV, except for cases with atelectasis. The contouring of the "primary GTV" within pulmonary tissue should be done using a lung window setting with the tissue density corresponding to the level of –750 HU and a window width of 850 HU recommended by Harris et al. [3, 11]. In case of the use of commercial planning systems with the density scales not corresponding to Hounsfield units, a standardisation of the CT window setting for the needs of treatment planning within each department is recommended [3].

Tumours with atelectasis remain a special and unresolved problem in GTV delineation. Sometimes it is impossible to distinguish between both components and such cases are considered as unsuitable for 3-D conformal radiotherapy techniques. The radiologists' opinion should be asked in such cases. In many cases a reasonable clinical compromise can be achieved. Some authors indicate that the use of special CT window setting with a width of 150 HU and a level of 50 HU ("liver window") could allow to distinguish both components [3]. Sometimes prior laser, or brachyterapy, can resolve the atelectasis. We recommend, in cases of minor component of atelectasis and/or possibility to encompass it with respect of dose constraints for critical structures, to consider the entire abnormality as the GTV. It minimises the risk of missing the tumour and at present it is a necessary and reasonable compromise. PET is also considered as a useful tool for the distinction of tumours from atelectasis, allowing, in many cases, to decrease the size of portals in comparison with treatment planning guided by CT only [12]. PET overestimates the tumour volume in case of an inflammatory process. Therefore, if the atelectasis is associated (as it is frequently seen) with any degree of inflammation, PET can also give inaccurate results. Lung cancer causing atelectasis remains a continual challenge for radiation oncologists and precise GTV delineation in such cases is actually not possible today.

Magnetic resonance imaging is not in routine use for GTV determination. It is only as accurate as CT in the

evaluation of the mediastinum. It is more accurate in the evaluation of the pulmonary hila, however this advantage is not commonly exploited [13].

The use of PET in the GTV determination really improves on accuracy, especially for mediastinal nodes. Additionally, the use of PET for staging of patients with NSCLC improves treatment results after radical radiotherapy, which is related to the stage migration resulting from a new method used [14]. Accuracy of PET in the detection of metastases in the mediastinal lymph nodes is about 90-95% [8, 14]. Despite a certain number of problems with PET routine use in radiotherapy planning, such as the high cost of method, overestimation of GTV in case of associated inflammatory processes, technical problems with matching images with 3-D CT images, impossibility of detection of nodal micro-metastases and low reliability for pulmonary hila, it is a growing interest on implementation of this method for the GTV definition [8, 10, 12].

Clinical target volume (CTV) definition

The CTV according to ICRU Report 50 criteria is defined as "a tissue volume that contains a demonstrable GTV and/or subclinical malignant disease that must be eliminated" [1]. Besides the GTV it contains the subclinical disease considered as microscopic malignant spread around the GTV and regional lymphatic drainage area as elective nodal irradiation volume.

The microscopic tumour extension as a margin around the GTV is difficult to evaluate, because there is no available imaging technique allowing us to measure it directly. Giraud et al. [15] have evaluated microscopic extension of the disease around macroscopic borders of tumours in surgical resection specimens. They found that usual margins around GTV of 5 mm can be inadequate for CTV creation and postulate to increase them to 8 mm for adenocarcinoma and 6 mm for squamous cell carcinoma in order to cover the microscopic extension with a probability of 95%. Obviously, it is of crucial importance to use the CT scanning with adequate resolution and thin slices and appropriate window/level setting, which probably allows to decrease margins for CTV creation, but the exact dimension can not be, at present, measured by radiological means. Therefore, respecting measures for adequate CT resolution and window setting, 5 mm margins for CTV delineation are also a reasonable clinical compromise. Giraud et al. [15] have also agreed with this solution for good quality CT scanning. Spiculated tumour margins are associated with greater microscopic extension [15], and usually they are included in CTV, but sometimes it could be a result of an inflammatory processes and there are no reliable imaging methods for determining exact tumour borders in such cases. The exact differentiation between GTV and CTV is of capital importance if IMRT techniques are aimed to deliver different dose per fraction levels for macroscopic and microscopic disease extension.

The CTV in radiotherapy for NSCLC includes also elective nodal irradiation (ENI) volume. It is related to the area of lymphatic drainage, in which the metastases were not detected by radiological means, but clinical and surgical data indicate a high probability of microscopic invasion. So, the ENI volume, as a part of the CTV, remains an anatomic-clinical concept and now the necessity of ENI is questionable. The opponents of ENI may argue that NSCLC is known for its highly distant metastatic potential and one could consider total body as the CTV and an eradication of such an extent of the disease by radiotherapy is not a conceivable idea. So, mediastinal ENI volume could appear as a result of a clinical compromise between the need of eradication of

Table I. N2 lymph node stations for lung cancer staging [28]

Lymph nodes group	Location
Group 1: Highest mediastinal lymph nodes	Above a horizontal line at the upper rime of the bracheocephalic vein ascending to the left, where it crosses the trachea at its midline
Group 2: Upper paratracheal lymph nodes	Above the upper margin of the aortic arch and below the inferior boundary of group 1 location
Group 3: Prevascular and retrotracheal lymph nodes	Pre- and retrotracheal
Group 4: Lower paratracheal lymph nodes	Tracheo-bronchial angles, azygos vein and main bronchi within mediastinal pleural envelope
Group 5: Subaortic (A-P window) lymph nodes	At the aortic-pulmonary window
Group 6: Para-aortic lymph nodes	Anterior and lateral to the ascending aorta, aortic arch or the innominate artery
Group 7: Subcarinal lymph nodes	Caudal and adjacent to the carina
Group 8: Paraoesophageal lymph nodes	Adjacent to the wall of the oesophagus, excluding subcarinal nodes
Group 9: Pulmonary ligament lymph nodes	Within the pulmonary ligament, including those of the lower part of pulmonary veins

subclinical disease and acceptable toxicity. The exact extent of the ENI is debated and its impact on survival is not proven. The concept of ENI was strongly supported by the findings from RTOG studies, showing a strong impact on survival and local control of proper inclusion of the mediastinal area, including contralateral hilum in radiation fields [16]. These findings led to the guidelines concerning the irradiation volume, which have influenced treatment policy for NSCLC up to date. It was stated that: "...for upper and middle lobe lesions, the mediastinal field should include 5 cm below the carina and supraclavicular areas. For lower lobe lesions, the lower margin of the field is the diaphragm..." [17]. On the other hand, it has been proven for NSCLC that the local control rate is disappointingly low (below 20%), if conventional radiation doses are employed [18]. For patients with the early stages of the disease with poor pulmonary function tests, omission of the ENI did not result in a significantly increased regional (outside irradiation field) failure rate and survival was not compromised by such a policy [19-22]. A large number of the dose escalation studies using conformal techniques were performed and the ENI revealed to be the largest contributor to the pulmonary and oesophageal toxicity [21-23]. Chemotherapy is largely employed in the management of NSCLC. Recent randomized studies have revealed that the concurrent use of radiotherapy and chemotherapy improves survival in comparison with sequential administration of both modalities [24, 25]. However, this improvement in survival is associated with significantly increased acute pulmonary and oesophageal toxicity [26]. Thereafter, some authors implement chemoradiation and/or dose escalation studies using involved-fields irradiation, based on the concept that chemotherapy may eradicate micrometastases and ENI could reduce the therapeutic ratio by increasing toxicity. The preliminary results of such an approach seem promising with no increasing rate of out-field nodal failure [10]. Omission of the ENI remains problematic, because, as it was stated above, there are no absolutely reliable diagnostic methods allowing to exclude the presence of nodal occult metastases. Longer follow-up and larger data are necessary to affirm the safety of this treatment policy. On the other hand the use of PET for treatment planning in NSCLC may improve evaluation of the extent of the disease and minimise the risk of omission of occult metastases [10]. In the absence of such advanced technology, an ENI volume could be reduced to the regions of the highest probability of nodal metastatic invasion. Some authors systematically include the hilar region to involved-fields radiotherapy for III stage patients, because of the high probability of metastatic invasion and the low reliability of CT, and even PET, for the evaluation of this region [8, 9, 10, 13]. For 3 years we have held to a protocol of the limited ENI for stage III patients. It is based on surgical and radiological data concerning the probability of nodal invasion [7, 27]. We systematically include in the limited ENI volume, considered here as the CTV, the ipsilateral hilum, subcarinal nodes (group 7), ipsilateral lower paratracheal (group 4) and pre- and retrotracheal nodes below upper margin of the aortic arch (group 3). The aortic-pulmonary window (group 5) and the right tracheo-bronchial angle (group 4) nodes are included in the CTV regardless of the site (right or left) of the tumour. Other nodal groups, if uninvolved, such as the upper paratracheal (2) and highest mediastinal (1) groups and paraoesophageal and pulmonary ligament nodes for lower lobes are not included in the CTV (for N2 lymph nodes stations definition for lung cancer staging, see Table I) [28]. In the 3-year follow-up period we have not observed any outside radiation-port nodal failure in the absence of local relapse and the volume of irradiated lung was reduced, as compared to the traditional fields, as defined by Rockman et al. [17].

A special problem for target volume's definition is adjuvant postoperative radiotherapy for NSCLC. The GTV is not delineated, and the extent of the CTV is certainly, regarding data on toxicity of postoperative radiotherapy, to be reconsidered. In the PORT meta-analysis it has been suggested that the excess mortality in irradiated patients, especially in early stages, may be reduced by careful patient selection, better treatment quality and probably also by the reduction of irradiated volumes [29]. Regarding the poor survival of patients with contralateral nodal (N3) invasion, the inclusion of contralateral nodes in the CTV is probably not justified [7]. In our Institution the protocol of the limited ENI, formulated as above, is ongoing for pN2 patients.

If there are no uniformly accepted guidelines concerning the use and the extent of the ENI, the strict formulation and respect of rules regarding CTV determination should be followed in each radiation oncology department with a view on facilitating data comparison.

Planning Target Volume (PTV) definition

The PTV according to ICRU Report 50 criteria is defined as "a geometrical concept used for treatment planning, and it is defined to select appropriate beam sizes and beam arrangements, to ensure that the prescribed dose is actually delivered to the CTV" [1]. A new ICRU Report 62 (supplement to ICRU 50) [2] detailed the data necessary to define margins between CTV and PTV introducing a concept of the Internal Margins (IM) related to the physiologic movements of the CTV and the Set-up Margins (SM) taking into account all uncertainties in patient-beam positioning. IM and SM are to be added to the CTV for the PTV determination [2].

Determination of IM is the real challenge in conformal radiotherapy for NSCLC. The heart and the great vessels beat, but this especially concerns respiratory movements – the factual major source of uncertainty. Respiratory movements differ in relation to the CTV location and change with direction of motion. Movements in the craniocaudal direction are larger than in the transversal plan and can exceed 1 cm. Ekberg et al. [30] postulate the increase of margins in the craniocaudal direction to 15 mm, or taking individual measures for

each patient. Many advanced technologies are investigated in order to eliminate the respiratory movements during the treatment planning and delivery. They consist grossly of treatment delivery in one precise phase of respiration [31]. Active breathing control and similar methods seem to be the melody of the nearest future, because many companies develop treatment planning and delivery systems allowing to treat patients in full control of respiratory movements. Respiratory mobility is of special importance for involved-fields techniques, because of increased risk of missing the CTV. Therefore, margins for nodal mediastinal mobility were evaluated. Margins of 5 mm seem sufficient at this level, probably except for subcarinal nodes, as this region needs further evaluation due to presumed greater mobility of the carina [32].

Set-up margins are related to mechanic uncertainties of the equipment, variations in patient positioning, transfer set-up errors in the CT – simulator – accelerator axis, human error and dosimetric uncertainties [2]. These latter are of a special interest for lung cancer treatment planning. Radiation oncologists could be pleased with treatment plans prepared for lung cancer with high energy photons. However, a penumbra areas are probably underestimated by commercial planning systems, because of the limited accuracy of penumbras calculated by existing dose calculation models in low density materials (e.g. lung) at high energies (15 MV et up) [33, 34]. The choice of energy for lung cancer conformal radiotherapy should take these facts into account.

Data concerning all these listed factors should be collected in each radiotherapy department for internal and set-up inaccuracy and the final decision on dimension of margins for PTV determination should be based on this knowledge.

Conclusions

In a number of areas we are still facing more queries than answers in order to define target volumes for radiotherapy of NSCLC. Most problems related to the target volumes definition in radiotherapy for NSCLC follow no precise, commonly accepted rules. In case of unproven clinical strategies special attention should be focused on creating detailed departmental protocols in order to avoid any errors and to find the best treatment policy for the future. Each department should be consistent in its approach to target contouring and definition. Data collected from these clinical experiences could form the basis for future guidelines or randomized studies.

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