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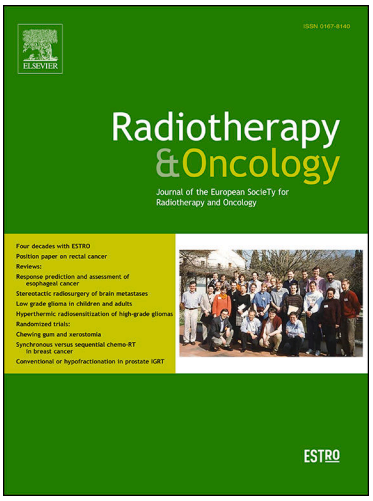

Original Article

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ESTRO ACROP guidelines for Target Volume Definition in the thoracic radiation treatment of Small cell lung cancer

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Abstract

Radiotherapy (RT) plays a major role in the treatment of small cell lung cancer (SCLC). Therefore, the ACROP committee was asked by ESTRO to provide recommendations on target volume delineation for standard clinical scenarios in definitive (chemo)-radiotherapy (CRT), adjuvant RT for stages I-III SCLC and consolidation thoracic RT for stage IV disease.

The aim of these guidelines is to standardise and optimise the process of RT treatment planning for clinical practice and prospective studies. The process for the development of the guidelines included the evaluation of a structured questionnaire followed by a consensus discussion, voting and writing process within the committee.

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Firstly, we provide recommendations for both the imaging to be performed as part of the diagnostic work-up and for the RT planning process. Secondly, recommendations are made for target volume delineation including delineation of the primary gross tumour volume (GTV) and lymph node GTV and clinical tumour volume (CTV) expansion in the context of definitive and adjuvant RT. With regard to internal target volume (ITV) and planning target volume (PTV) definitions, we make recommendations about the management of geometric uncertainties and target motion. Finally, we provide our opinions on organ at risk (OAR) delineation and organisational issues to be considered.

Introduction

Lung cancer is the most common cancer diagnosis (about 1.8 million new cases per year), and the leading cause of cancer death (1.59 million deaths per year) in the world [1]. Currently, small-cell lung cancer (SCLC) accounts for 13% of all lung cancers, and more than 2/3 of the patients present with metastatic disease. As opposed to NSCLC, patients often have a bulky mediastinal disease at presentation, frequently with involvement of bilateral mediastinal lymph nodes. After staging procedures, SCLC used to be classified as 'limited' or 'extensive' stage according to the Veterans Administration Lung Cancer Study Group Classification [2]. Historically 'limited stage' disease was defined as disease confined to the involved hemithorax including the regional lymph nodes (mediastinum, ipsilateral and contralateral hilar regions, ipsilateral supraclavicular fossa), thus theoretically treatable with RT to a curative intent dose. The International Association for the Study of Lung Cancer (IASLC) has since published recommendations to use the lung TNM staging classification for SCLC patients [3]. The 7th and now the 8th lung TNM staging classifications are more accurate in identifying prognostic patient subgroups and their use has now become standard [3,4]. However the Veterans Administration Lung Cancer Study Group Classification continues to be used by many clinicians in the routine setting.

As SCLC has a high propensity for early metastatic dissemination, due to rapid doubling-time, chemotherapy remains the cornerstone of treatment [5-9]. However, RT plays a major role in both the curative and palliative settings. Even though response rates to both chemotherapy and RT are high, the majority of patients will relapse after treatment.

The current state-of-the-art treatment for patients with stage I-III disease amenable to curative RT, involves platinum-etoposide based chemotherapy (4-6 cycles), administered concomitantly with thoracic RT [6-9]. RT should be initiated as early as possible, ideally concomitant to the first or second cycle of chemotherapy in fit patients [10-14]. A prospective randomised phase III study from Korea has shown that thoracic RT starting concomitantly with the third cycle of chemotherapy appeared to be non-inferior to thoracic RT initiated concomitantly with the first cycle [15].

The recommended thoracic RT dose is 45 Gy in 30 twice-daily fractions delivered over 3 weeks; 66 Gy in 33 once-daily fractions can be considered when delivery of twice-daily RT is not possible because of patient choice or departmental logistics [10-13]. In case of large volume tumours, choice of once-daily RT will be risk adapted to the individual patient, taking into account dose constraints for organs at risk (expert opinion). Five-year survival rates of 25-35% have been reported in patients with stage I-III disease following curative intent treatment [12,13 Faivre-Finn Kubota]. Because of the high risk of brain metastases, prophylactic cranial irradiation (PCI) is indicated in patients without progressive disease after CRT in stage I-III SCLC [6-9,16-18]. Even though the PCI meta-analysis has shown an improved survival in stage I-III patients undergoing PCI, one should be prudent in prescribing it in patients at higher risk of neurocognitive toxicity such as patients over 70 years of age [19].

Unfortunately, most patients relapse within the first two years and there are limited systemic treatment options in the second-line setting [6-8], in contrast to treatment options in NSCLC. The majority of outcome advances reported within the last years for patients with stage IV SCLC were principally due to developments in RT, although data on the role of immunotherapy in SCLC are now emerging [20,21]. In several European countries, there has been a change in standard of care for stage IV disease to use of chemo-immunotherapy regimens as first-line treatment [22,23]. The integration of consolidation thoracic RT with the change to these combination systemic therapies highlights the potential for the additive effect of local therapy and combination chemo-immunotherapy to impact on clinical outcomes, and new studies are warranted. Due to the contrasting results of 2 randomized trials evaluating PCI in stage IV disease [24-25], there is a need for a new trial comparing PCI (with or without hippocampal sparing) to MRI surveillance in the combination chemo-immunotherapy era.

This ESTRO-ACROP target volume definition initiative highlights the fact that RT quality control may play an important role in improving outcomes [13,26]. RT protocol deviations have been associated with poorer overall survival [27,28]. As modern planning techniques have become more conformal, accurate delineation of target volumes and OAR have become increasingly important. This ESTRO-ACROP guideline, aims to provide an overview of existing delineation strategies based on the current literature in SCLC. Here, we address delineation for curative intent and adjuvant RT in stage I-III SCLC as well as consolidation thoracic RT in stage IV SCLC.

Methodology

All recommendations in this manuscript are the result of the evaluation of a structured questionnaire followed by a consensus discussion and voting procedure within the small cell and non-small cell lung cancer committee [29]. This resulted in a categorisation of

recommendations in four categories: Mandatory (M), Recommended (R), Optional (O), or Discouraged (D). This procedure was followed by a writing process, in which results of additional literature search were used as appropriate and a final discussion and review by the committee members.

1. Recommendations: Chemo-Radiotherapy (CRT) in stage I-III SCLC

Diagnostics / Staging Imaging

Treatment should not start before cytological, or optimally, histological diagnosis of SCLC has been confirmed (M). In preparation of target volume delineation for CRT in patients with stage I-III SCLC, a diagnostic chest and upper abdomen CT with intravenous (IV) contrast (in the absence of contra-indications) is considered mandatory (M) and brain imaging to exclude intracranial metastatic disease (M). Even though evidence supporting the role of a diagnostic FDG-PET-CT and its impact on treatment decisions is limited [30], a FDG-PET-CT is recommended for the purpose of assisting target volume delineation (R). As in NSCLC, diagnostic imaging should be performed within 3 weeks before the start of treatment (R).

Concomitant CRT is recommended as the standard of care in fit patients, but in case of treatment with sequential CRT, it is mandatory (M) to repeat the chest and upper abdomen CT with IV contrast and recommended [R] to perform brain imaging after the last cycle of chemotherapy and before the start of RT.

As most tumours are central and bulky, often invading adjacent vasculature, additional workup may be performed beyond standard diagnostic imaging procedures, with regards to mediastinal lymph node involvement (O). There are limited data available on the positive and negative predictive values of mediastinal staging of both CT and PET-CT in SCLC [6-9,30]. As tumour grows under the bronchial mucosa, bronchial biopsy may be negative and crush artefacts or necrosis may also render diagnosis difficult. Endobronchial ultrasound (EBUS) guided needle aspiration and/or esophageal endoscopic ultrasound (EUS) with guided fine-needle aspiration (FNA) or mediastinoscopy can be useful for diagnosis or to evaluate more precisely the mediastinal staging [31-33]. This is particularly important when such staging may have a significant impact on tumour volume delineation, for instance in case of FDG avid lymph node(s) at a distance from primary disease. However these investigations should preferably not delay treatment.

Planning-CT (cloned from NSCLC)

Even if a diagnostic CT with IV contrast is available, a dedicated planning CT should be performed with the patient in the treatment position with IV contrast (R) unless medically contra-indicated. The lack of IV contrast can result in reduced visualisation and

distinction of tumour boundaries from surrounding structures such as blood vessels and lymph nodes. The slice thickness should not exceed 3 mm, the scan range should cover at least from cricoid to L3. All recommendations about the planning CT procedure to take into account respiratory motion are detailed in the NSCLC ESTRO ACROP guidelines [29].

Additional imaging for RT-Planning

Even with a staging PET-CT scan being recommended (R), a planning PET-CT scan is optional (O) and if performed, it should be done with the patient in the treatment position before any systemic therapy (if administered prior to RT). Considerable tumour and nodal shrinkage can be observed in patients after one cycle of chemotherapy. Any imaging that is not acquired in treatment position should not be co-registered with planning CT in the treatment planning system (D). Even when co-registration cannot be performed, visual comparison between pre-treatment PET-CT (as well as IV contrast chest CT scan) and planning CT is very useful.

GTV and CTV

The GTV is defined as macroscopic primary tumour (GTVp) and involved lymph nodes (GTVn). The GTVn is based on the involved lymph nodes before the start of chemotherapy (M). All pathologically confirmed lymph nodes (if available) should be delineated (R). Also, all lymph nodes considered pathological on CT (short axis $\geq$10 mm) or PET-CT (focal FDG accumulation above blood pool) should be included (M). It is our expert recommendation that consideration should be given to the inclusion of adjacent suspect clusters of smaller LN (short axis < 10 mm).

Delineation of the GTV, including the primary (GTVp) and lymph nodes (GTVn), should be performed on a dedicated planning CT with the patient in the radiotherapy treatment position (M), with both lung and soft tissue windowing being used to aid delineation (R). Ideally GTVp and GTVn should be contoured separately (O). However in the setting of SCLC, it may be difficult to distinguish the two volumes from each other and in that case a single encompassing GTV can be delineated.

Ideally the GTV should be contoured taking respiratory motion into account using a 4DCT or breath hold CT scan for delineation (R). However where such motion management techniques are unavailable, GTV delineation can be performed on a free-breathing planning CT scan (O). For all considerations and details, regarding management of respiratory motion in the treatment plan, readers should refer to NSCLC ESTRO ACROP guidelines [29].

As discussed in the introduction, thoracic RT should be initiated as early as possible, with the first or second cycle of chemotherapy in fit patients [10,11,13-15]. In case of systemic therapy commencing prior to RT, the accuracy of GTV delineation on a

planning CT scan acquired after the start of systemic therapy, might be subject to more inter-observer variation compared to delineation on a planning CT acquired before the start of systemic treatment.

Delineation of the GTVp should take into account any prior shrinkage due to systemic chemotherapy given prior to starting RT. A prospective randomized phase III study compared outcome of 309 SCLC patients who were assigned to receive radical RT to either the pre-chemotherapy or post-chemotherapy GTVp, commencing after 2 cycles of etoposide and cisplatin. The lymph node regions (GTVn) involved before initiation of chemotherapy were included in the radiation volume in both arms, even when the lymph node(s) could not be visualised on CT after induction chemotherapy [34]. There was no difference in 5 year loco-regional progression free survival rate (around 60% in both arms) or 5 year overall survival rate (24 and 26% respectively), confirming that RT can be limited to post-chemotherapy GTVp extent while pre-chemotherapy nodal extent should be included in the irradiated GTVn (discussed further below).

The GTVp interfacing with the lung parenchyma should be assessed at the time of treatment planning to take into account tumour reduction with prior systemic therapy, in order to reduce lung parenchyma irradiation. If the GTV is infiltrating into the mediastinum, the pre-chemotherapy volume of the interface between GTV and mediastinum should be delineated, whereas the post-chemotherapy volume of the interface between the GTV and lung parenchyma should be contoured (R based on expert opinion). As previously stated, adaptation of the GTV based on pre-treatment FDG-PET information is recommended (R).

In the absence of complete response to prior systemic therapy, the CTV comprises the GTV or motion managed GTV with a 5 mm margin in all directions to take into account microscopic spread. It should be manually adapted to the surrounding anatomy, e.g. manually edited away from anatomical structures such as vertebra or heart (M).

Based on a consensus of expert thoracic radiation oncologists involved in this guideline, in the case of complete response (CR) to systemic therapy of the primary tumour and therefore inability to delineate a GTVp, a CTVp should be delineated instead based on pre-treatment imaging (R).In case of complete response to systemic therapy of lymph nodes observed on a RT planning CT scan, there are two options when contouring CTVn instead of GTVn based on a consensus of expert thoracic radiation oncologists:

Option 1: CTVn corresponds to the geometric expansion of 5-6 mm around the pre-treatment nodal GTV particularly in terms of cranio-caudal extension. This option should be favoured in case of bulky mediastinal tumours. Manual editing of the CTV away from structures such as the heart and vertebra is recommended (R); the manual editing away from large vessels, esophagus or airways is more controversial (O).

Option 2: CTVn corresponds to the whole anatomical area (lymph node station) of pre-systemic therapy involved nodes, defined using CT-scan based atlases, taking into consideration [35, 36] the major modifications brought by the TNM Atlas 7th edition in terms of lymph node region definitions [37] (R). The remarks regarding manual editing of CTV in option 1 can also be applied in option 2.

As in NSCLC, elective nodal irradiation in general is not recommended and inclusion of uninvolved areas between involved stations and primary tumour volume (especially the hilum) is optional (O). In case of upper mediastinal lymph node involvement on diagnostic CT (i.e. involvement of nodal station 2 or 3A) and no pre-treatment PET scan, the ipsilateral supraclavicular nodal region can be considered for inclusion in the CTVn, as the risk of supraclavicular failure is >10% [38]. However further inclusion of elective lymph nodes in the CTVn is not recommended (D).

PTV

As in NSCLC, a margin should be applied around the CTV to create the PTV to account for the geometric uncertainties (M) according to current ICRU recommendations. There are no differences in terms of motion patterns between SCLC and NSCLC. Sources of uncertainties include delineation errors [39], the inter- and intra-fraction patient (setup), tumour (baseline shift) and tumour motion-related errors (see below). These should ideally be quantified in each individual RT department for the relevant treatment settings (R).

OARs

For planning of fractionated RT in lung cancer, the organs at risk to be contoured are: the lungs (both lungs separately plus both lungs together excluding the CTV or GTV), the whole heart including the pericardial sac, the oesophagus from cricoid to esophageal-gastric junction and the spinal canal (as PRV for the spinal cord) (M). The central bronchial tree and chest wall do not need to be defined for routine RT with standard of care dose/fractionation. However delineation of trachea and bronchial tree may be useful to match cone beams CT and reference planning CT scans for image guided RT.

Adaptive Re-Planning

As SCLC is particularly responsive to CRT, leading to important volume changes during the course of the irradiation in the primary tumour, adaptive re-planning may be performed on an individual patient basis. Such changes have been quantified in a small retrospective study [40]. The authors reported a GTVp reduction > 50% at the end of the first week of CRT. The authors concluded that most of GTVp shrinkage occurred during the first week of CRT. Such adaptation of target volumes should not be applied to the GTVn as discussed above in relation to systemic therapy prior to CRT. Treatment

should not be interrupted, as the risk of repopulation is of particular concern in SCLC [5].

2. Recommendations: Post-operative RT in resected SCLC

There are limited data on resected SCLC as most patients are diagnosed with advanced or locally advanced disease and are not amenable to surgery. Two randomised trials have assessed the role of surgery in SCLC. The first trial was performed before the era of chemotherapy, and is therefore of limited value. However the second trial investigated the role of surgery after neoadjuvant chemotherapy followed by postoperative thoracic RT and PCI [41,42]. The negative results of both studies led to the conclusion that surgery has no place in the treatment of SCLC. However, there has been a reappraisal of the role surgery in the past 5 years, in early-stage SCLC (stage I and II) [6-8]. Some of these patients present with a small peripheral nodule without hilar or mediastinal lymphadenopathy on CT scan and/or PETCT, and correspond to “incidentally resected” SCLC patients. We know that in such cases, the quality of surgery, especially nodal exploration, can be suboptimal, so that patients reported as pT1 N0 M0 and pT2 N0 M0 SCLCs may be understaged. Whether patients with resected SCLC should be considered for post-operative RT, is a controversial question [17]. There is consensus on post operative RT after R1 or R2 resection ((R), expert opinion based on practice in NSCLC). Following resection of SCLC, post-operative thoracic RT and PCI should be discussed with the patient in the context of shared decision-making [17].

Another area of controversy is the thoracic volume that should be irradiated post-operatively. The pre-surgery chest CT with IV contrast, PET CT if acquired, surgical report and pathological report should be carefully reviewed by the multidisciplinary team. To comply with the definition of complete resection, the International Association for the Study of Lung Cancer (IASLC) has defined adequate lymph node exploration as at least three mediastinal lymph node stations and the sampling of at least three hilar lymph node stations, depending on the location of the primary tumour [43]. As there is a preferential route of mediastinal dissemination for primaries in each lobe, based on large surgical series of resected NSCLC, nodal irradiation should vary according to nodal stations at risk of involvement, dependent on primary tumour location [29,44] ((R) expert opinion based on practice in NSCLC).

When post-operative RT (PORT) is performed, the CTVn should consist of the **resected involved** mediastinal and hilar lymph node regions as well as the bronchial stump and station 7. In case of pre-operative chemotherapy, initially involved station should be included in the CTVn, even in case of downstaging. All the lymph nodes between two

non-contiguous node stations that are involved should be included in the CTV ((R) expert opinion from the panel).

If the resected patient has not had adequate nodal exploration as recommended by surgical guidelines, and no nodal involvement based of pre-treatment imaging, there are two options that should be discussed within the multi-disciplinary board (MDB):

Option 1: Surveillance with 3 monthly CT scanning (preferred option).

Option 2: PORT of nodal stations at risk of involvement, dependent on primary tumour location.

3. Recommendations: Stereotactic body RT (SBRT) for early stage SCLC

Even though stage I SCLC is rare, SBRT may be an option in inoperable patients, and should be discussed within the multidisciplinary team [9, 45-48]. Patients with early lung cancer can also be treated with combined CRT with good results as shown in a recent analysis [49]. In coming years we expect a larger proportion of lung cancer patients, including SCLC, to be diagnosed earlier due to the implementation of lung cancer screening [6]. Treatment should be performed according to the ESTRO ACROP guidelines for early stage NSCLC [50]. SBRT should be performed before chemotherapy, as tumours may not be adequately delineated in case of good or complete radiological response after chemotherapy.

4. Recommendations for Thoracic RT in stage IV SCLC

Intrathoracic tumour control is an important aim in patients with metastatic SCLC. In the EORTC randomized study evaluating PCI in this group of patients, it was shown that 75% of these patients had persisting intrathoracic disease after chemotherapy and ~90% had intrathoracic disease progression within the first year after diagnosis [25]. The addition of consolidation thoracic RT (TRT) after 4-6 cycles of chemotherapy was evaluated in a European phase III randomised trial [51], two randomized phase II trials and data was pooled in a meta-analysis [52-54]. In the randomised phase III study, TRT (30 Gy in 10 fractions) in addition to PCI led to a significant reduction in intrathoracic recurrence compared to PCI alone in patients who had initial disease response to chemotherapy. The primary endpoint of improved overall survival at 1 year in all patients was not met; however there was a significant improvement in overall survival at 2 years (13% versus 3%). A subgroup analysis demonstrated the addition of consolidation TRT improved 1-year survival significantly in patients with residual intra-

thoracic disease (rather than intra-thoracic complete response). As there are limited second line treatment options, consolidation TRT should be considered for patients who respond to first-line systemic treatment but have residual intra-thoracic disease (R). This strategy has been widely adopted in Europe [18,55].

Based on the European phase III trial, the GTVp should include the post-chemotherapy volume (R). Hilar and mediastinal nodes rather than lymph node stations that were considered initially involved should also be included in the target volume and delineated as CTVn. The volume reduction of lymph nodes should be taken into consideration but the cranio-caudal extent should be defined based on pre-chemotherapy imaging (R). The other option is inclusion of whole anatomical nodal stations, but this approach will lead to large treatment volumes, with the risk of significant toxicity.

The first line treatment in stage IV small cell lung cancer is changing rapidly, with immunotherapy being administered in combination with chemotherapy [22,23]. It should be outlined that we have only limited data on the safety of combining immunotherapy with TRT in this group of patients, as no TRT was given in the two randomised trials that established chemo-immunotherapy as standard of care compared to chemotherapy. There are however on-going studies evaluating the use of concomitant CRT and immunotherapy in SCLC that will provide safety data on combination treatments in the coming years.

Organisation/Responsibilities

As for NSCLC, it is strongly recommended to develop departmental protocols for delineation (M), preferably with the use of atlases (R) [29,36,37]. A collection of sources for atlas based delineation (specific papers, atlases and trial protocols) can be found in the appendix. Several articles have also reported the importance of RT quality assurance in randomized trials investigating localised SCLC [13,26,27,56]. For physicians and radiation therapists (or RTTs) in training, peer review of delineations by an experienced colleague is mandatory (M). Additionally, hands-on training in an experienced centre or by participation in teaching courses should be considered (O).

All tumour volume delineation (GTVs, CTVs) should be performed by radiation oncologists specialised in lung cancer (M), however the contouring of OARs may be delegated to RTTs, with or without the aid of automated (artificial intelligence) tools, after appropriate training in certain centres and/or countries (O) [57].

Final approval of all contours before planning must be completed by a radiation oncologist (M). Additional review by other radiation oncologists is recommended (R).

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Conflict of interest statement

The following authors declare that they have competing interests:

Rafal Dziadziuszko: AstraZeneca, Pfizer, Roche, Seattle Genetics,Takeda (Advisory Boards)

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Highlights

• Thoracic target volume definition in small cell lung cancer (SCLC) can be quite challenging

•Addressed through different clinical scenarios: concomitant chemoradiotherapy (CRT) starting on cycle1, concomitant CRT starting after induction chemotherapy or sequential chemoradiotherapy or post-operative radiotherapy in stages I-III SCLC and consolidation thoracic radiotherapy in stage IV.

•possible role of stereotactic radiotherapy in early SCLC

• In case of induction chemotherapy, given prior to starting RT, reduced volume SCLC primary tumour volume (post CT GTVp) should be considered whereas pre-chemotherapy nodal extent should be considered for nodal disease (pre CT GTVn)

Table of recommendations regarding radiotherapy strategies in SCLC

Categorisation of recommendations in four categories: Mandatory (M), Recommended (R), Optional (O) or Discouraged (D).

RT strategies in SCLC	Timing	Target Volume	Cate reco
1. **CRT for stage I-III SCLC pts**	. Concomitant to 1st ChT cycle in fit patients	GTVp and GTVn based on CT scan and PET CT For CTV and PTV: refer to manuscript	R 10,
	. Concomitant to 2nd ChT cycle in fit patients	Post-CT GTVp and preCT GTVn based on planning CT scan, pre-ChT CT scan and PET CT For CTV and PTV: refer to manuscript	R 12,
	. Concomitant to 3rd ChT cycle in fit patients with bulky tumour	Post-CT GTVp and preCT GTVn based on planning CT scan, pre-ChT CT scan and PET CT For CTV and PTV: refer to manuscript	O 15,
	. Sequential after 4 cycles of ChT in frail pts	Post-CT GTVp and preCT GTVn For CTV and PTV: refer to manuscript	R 6-9
2. **Postop RT in ypN1 and ypN2**	After surgery if preop ChT	. In case of pre-op ChT, initially involved station(s) should be included in the CTVn . CTVn =resected involved mediastinal and hilar lymph node regions as well as the bronchial stump and station 7 For PTV: refer to manuscript	Reco Timi Volu (29,4
Postop RT in pN1 and pN2	After ChT if surgery and postop ChT		
R1 or R2 resection			Expe
3. **SBRT for peripheral st I**	SBRT before ChT	ITVp No CTVp and for PTVp: refer to manuscript	O
4. **Consolidation RT in stage IV responders to**	Sequential after 4-6 cycles of ChT	. Residual intrathoracic disease Post ChT CTVp and Pre ChT CTVn = nodes considered initially involved, to be included in the target volume.	R (52 O (54

4-6 cycles of ChT		. No residual intrathoracic disease	O (52
	Sequential after ChT+IO		To b

Abbreviations: RT= Radiotherapy; CRT= chemoradiotherapy; ChT=Chemotherapy; GTVp= Gross Tumor volume of primary; GTVn= Gross Tumor volume of node(s); SBRT=Stereotactic Body RadioTherapy; pts=patients; IO=Immunotherapy

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