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Case report

The importance of image guided radiotherapy in small cell lung cancer: Case report and review of literature

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ABSTRACT

Aim: Describe the anatomical changes and tumor displacement due to a rapid response of a patient's small cell lung cancer (SCLC) during definitive chemoradiotherapy (CRT).
Background: The treatment for SCLC is based on CRT. If interfractional changes during RT are incorrectly assessed they might compromise adequate coverage of the tumor or increase dose to organs at risk. Image guided RT with cone-beam computed tomography (CBCT) allows to identify daily treatment variations.
Material and methods: Describe a SCLC case with rapid changes in size, shape and location of the primary tumor during RT.
Case report: A 62-year-old woman was diagnosed with SCLC with complete obstruction of the anterior and lingular bronchi and incomplete left thorax expansion due to a 12 × 15 cm mass. During CRT (45 Gy in 1.5 Gy per fraction, twice daily) the patient presented rapid tumor response, leading to resolution of bronchi obstruction and hemithorax expansion. Tumor shifted up to 4 cm from its original position. The identification of variations led to two new simulations and planning in a 3-week treatment course.
Conclusions: The complete radiological response was possible due to systematic monitoring of the tumor during CRT. We recommend frequent on-site image verification. Daily CBCT should be considered with pretreatment tumor obstruction, pleural effusion, atelectasis, large volumes or radiosensitive histology that might resolve early and rapidly and could lead to a miss of the tumor or increased toxicity. Further research should be made in replanning effect in coverage of microscopic disease since it increases uncertainty in this scenario.

1. Background

Small cell lung cancer (SCLC) accounts for about 10–15% of all lung cancer. In 2017, an estimated 29,654 new cases of SCLC occurred in the United States. Although the incidence of SCLC has been decreasing, the incidence in women is increasing and the male to female ratio is now 1:1.[1] SCLC biology is different from the more common non-SCLC, due to its rapid doubling time, higher growth fraction and early development of widespread metastases.[2] The treatment is mainly based on chemoradiotherapy (CRT). SCLC has also been recognized to be more responsive to radiotherapy (RT) than NSCLC, but the molecular basis for this responsiveness is yet unknown.[3]

Interfractional changes during RT have been reported in early and locally advanced disease and, if not correctly assessed, might compromise the adequate coverage of the planning target volume (PTV) or increase the planned dose to nearby organs at risk.[4] Interfractional setup shifts may be as high as 3 cm, especially if the tumor is associated to obstruction, atelectasis or pleural effusion, which can be reduced partially by respiratory motion control techniques.[5,6] Respiratory tumor motion control decreases the position uncertainty of the target and organs at risk. However, tumor response during a course of RT might resolve the airway pathway or lymphatic drainage obstruction, leading to drastic inter-fraction motion.[5]

Image-guided RT with modern verification systems, such as Cone-Beam Computed Tomography (CBCT), allows to systematically monitor treatment variations. It also enables physicians to incorporate variations and reoptimize the treatment plan as early as needed during the course of treatment. This process called

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"adaptive RT" (aRT) allows customized treatment plans re-optimization according to individualized target volume and anatomic variations due to day-to-day shifts or shrinkage associated to treatment response.[7,8]

Although aRT and new simulation allows radiation oncologists to individualize treatment, a problem to be considered is that new clinical target volume (CTV) might not include the original location or adjacent anatomical structure that were initially considered in the treatment volumes.[7] If only gross tumor shrinkage is considered to perform new volumes, there will potentially be a miss of coverage of the subclinical disease. Therefore, some argue that physicians must decide, based on previous clinical and imaging information, which healthy tissue with potential subclinical disease should be treated.[8,9]

2. Aim

Describe the anatomical changes and tumor displacement due to a rapid response of a patient's SCLC during definitive CRT.

3. Material and methods

In this report, we describe a case of a patient with SCLC with associated bronchial obstruction treated with concurrent CRT in which inter-fraction motion due to tumor response was so dramatic that different re-planning and re-optimizations were warranted. This case report exemplifies the importance of image-guided and adaptive RT in patients where tumor response is so important that conventional radiation system verification and planning might be insufficient.

4. Case report

A 62-year-old woman with heavy smoking history (41 pack-years) with no other known comorbidities, was admitted to our clinic in May 2017 due to respiratory distress and tachycardia. Initial workup included a chest X-ray which showed a left perihilar mass, followed by an image-guided biopsy which documented a neuroendocrine SCLC (chromogranin, sinaptofisine and CD56 stain was positive) with high Ki-67 expression (70%). A whole-body baseline ^{18}F-FDG PET-CT scan (Biograph 16HR, Siemens) performed at diagnosis revealed a left perihilar mass of approximately 60-mm × 42-mm diameter, the maximum standardized uptake value (SUVmax) was 8.6. The tumor involved the left pulmonary artery reducing importantly its diameter; likewise, it involved the inferior left bronchi without collapse, and extended to the anterior and lingular segmental bronchi with complete collapse. It showed associated superior lobar and lingular atelectasis. Complete work-up included a brain MRI which was negative to brain metastases. She was diagnosed with T4N0M0 (AJJC, CS IIIA) limited stage SCLC and scheduled for standard concurrent CRT.

Chemoradiotherapy with etoposide and cisplatin and 45 Gy in 30 fractions, administered twice daily (BID) in 1.5-Gy per fraction. The patient started treatment on June 21st and finished on July 14th, 2017. According to RTOG/EORTC radiation toxicity grading, only mild esophagitis was documented. After completing CRT, she received adjuvant chemotherapy with 3 cycles of etoposide and cisplatin. After the second cycle of adjuvant chemotherapy, she presented grade 3 neutropenia which resolved with no further complications with colony-stimulating growth factor.

A CT simulation scan of 3-mm-slice thickness was acquired with GE-CT 850 on June 15. Initial diagnostic studies showed a primary lung cancer of 12 × 15 cm diameter with complete obstruction of the anterior and lingular bronchi, secondary superior lobar and lingular bronchi collapse and left hemithorax with incomplete lung expansion (Fig. 1).

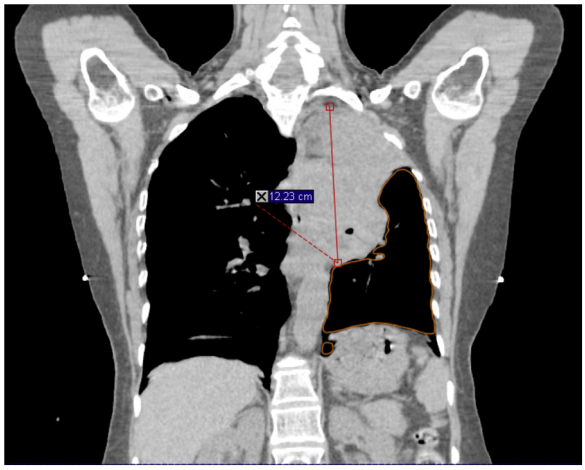

Fig. 1. Initial CT before CRT, upper and anterior left hemithorax completely occupied by left lung primary cancer.

Table 1
Patient tumor volume according to its schedule of radiation therapy; volume measured in cm^3 by cone beam - Ct, and its reduction according to inicial volume measured in cm^3.

Schedule of radiation therapy (fraction day)	Volume (cm^3)	Volume (cm)	Reduction
Initial volume	319.2	8.5	0%
3	314.98	8.4	1.32%
5	290.66	8.2	8.90%
7	230.26	7.6	27.86%
9	223.21	7.5	30.07%
New Ct simulation scan	235.85	7.7	26.11%
11	234.59	7.7	26.50%
13	205.24	7.3	35.70%
15	204.18	7.3	36.03%
17	126.93	6.2	60.23%
New Ct simulation scan	56.55	4.8	82.28%
18	56.55	4.8	82.28%
20	22.22	3.5	93%
21 and thereafter	No longer mesurable	–	–

CTV was contoured with a non-symmetrical 5 mm expansion of the gross tumor volume. An isotropic 5 mm CTV to planned target volume (PTV) expansion was made. Left hilum was included, but no elective mediastinal lymph nodes were included.

The patient received concurrent CRT with cisplatin and etoposide on June 21st. Patient's rapid tumor regression is recorded in Table 1. A 30% reduction can be noticed by fraction 9. At that time, we decided to resimulate and replan the treatment maintaining the CTV and PTV as similar as possible, since density inside the PTV was so different it might lead to inaccurate dose distribution (Fig. 2). Tumor response continued a steady rhythm (Table 1) and pathological retraction of the mediastinum gradually resolved, returning to its natural position. Bronchi obstruction release eventually led to a complete expansion of the hemithorax, and continuous tumor regression prompted an unexpected displacement of the GTV. By fraction 17, part of the posterior border of the GTV was outside the original PTV since it had shifted 1 cm posteriorly (Fig. 3). A new simulation and replanning were prompted to accomplish uncertainties.

The patient finished CRT schedule in July 2017, presenting only mild esophagitis, neither pneumonitis nor other acute or late radiation induced toxicities were documented.

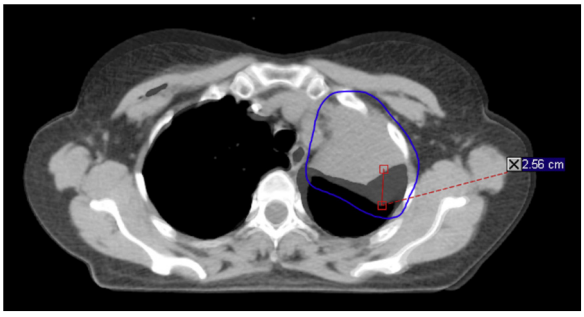

Fig. 2. Overlap and matching of CT simulation scan with CBCT at fraction number 9. A reduction of 2.5 cm can be noticed, with a corresponding reduction of 30%. Resimulation and replanning was performed to correct PTV (Blue) and account for dosimetric uncertainties associated to inside PTV tissues density and dose distribution. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

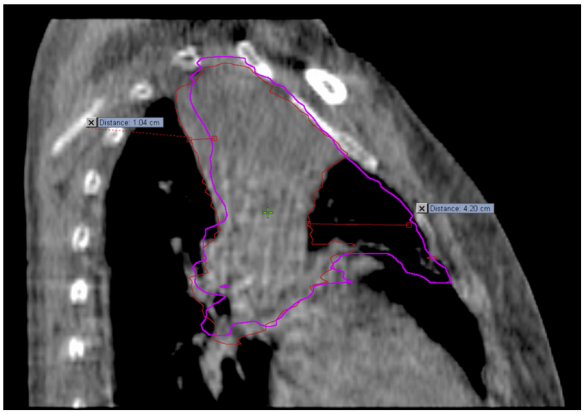

Fig. 3. Initial GTV (in fuchsia) from the CT simulation scan. GTV (in red) from the 17th CBCT. GTV has displaced by 1 cm posteriorly from its original position, which could lead to a marginal miss of the PTV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Our patient presented a complete radiological response to treatment, the two following PET CT scans with no evidence of disease. She had been scheduled to receive prophylactic cranial irradiation (PCI). Although primary tumor control was achieved with primary CRT, brain metastases were documented before PCI. Two months after completing whole-brain radiation therapy (37.5 Gy in 15 fractions), the follow-up MRI showed complete intracranial response. She continued with oncologic surveillance and was free from disease until she later developed liver, para-aortic lymph nodes and pancreatic metastases as detected on PET CT performed in April 2018. She received ipilimumab and nivolumab as per institutional protocol. Later, she developed and died from severe cholangitis in May 2018.

5. Discussion

Delivering ablative doses of RT while avoiding organs at risk remains the main challenge in radiation oncology, and is particularly meaningful in chest malignances. Tumor and organ respiratory motion, changes in patient anatomy, resolution of bronchi obstruction or pleural effusions, and weight loss when not adequately considered, might potentially lead to insufficient tumor coverage or additional radiation to normal tissues compared to what was previously planned or expected, resulting in inadequate tumor response or excessive toxicity. Studies have shown that tumor motion is mainly asynchronous[10] and unique for each tumor size, shape and patient. Therefore, respiratory motion, must always be addressed in lung cancer treatments. If not taken into consideration, artifacts and uncertainties in imaging will affect the whole treatment process diminishing the accuracy of radiation therapy either in planning or treatment delivery.[11,12]

Another way to increase the precision of RT is the use of on-board image guided radiation therapy (IGRT).[13] CBCT images, before delivering treatment fractions, allow radiation oncologist to account for geometric deviations from simulation tomography. The benefits of IGRT are very well described for many cancer sites[14] and small clinical trials have found the incidence of radiation pneumonitis might be lower when IGRT is used in non-SCLC.[15] Furthermore, IGRT techniques might also increase a tumor response. A series of 168 locally advanced NSCLC patients found a 13% increase in 2-year locoregional disease-free survival with daily CBCT compared to weekly MV portal imaging, with a reduction in acute grade 3 toxicity and any late toxicity.[16]

Daily IGRT with CBCT also yields the possibility of adaptive planning, proving useful information for clinicians to adapt RT plan for optimal patient setup and on-site recognition of anatomical or structural variations that, if not correctly addressed, would lead to a marginal miss or even a complete miss of the tumor volume as stated in this case report.

Intrathoracic anatomical changes during RT have been widely described. A study done in the Netherlands by Kwint et al. analyzed 226 patients with 1793 CBCT founding anatomical changes in over 70% of these patients, 9% of which required an adapted treatment plan to account for the changed anatomy. More importantly, most of the anatomical changes occurred in the first week (55%). In weeks 2, 3, 4 and 5, anatomical changes were observed in 16%, 15%, 8% and 6% of the patients, respectively.[17] On the other hand, Knap et al. reported that 1/3 of lung cancer patients undergoing CRT achieved significant tumor shrinkage at the end of RT. In this study 30% of the patients had SCLC histology.[18]

Dramatic tumor regression might lead to modification in RT dose distribution due to differences in electron densities of displaced tissues in the patient's body between fractions. Radiation dose distribution differs from air to solid tissue, and new planning is important to correct for those uncertainties. Therefore, adaptive RT will lead to a better dosimetry within PTV and maintain dose in organs at risk as originally planned. In our patient, after the first resimulation and replanning, continuous tumor regression and subsequent anatomical changes lead to the expansion of the hemithorax and mediastinum to return to its natural position. In the CT image, a posterior displacement of the tumor can be noticed, since the anterior lobes of the lung were previously collapsed as showed in Fig. 3. New subsequent simulation and planning were done. These periodic simulations enable ongoing alterations of the target volume to remain inside the PTV and exclude normal tissue that otherwise would have been inside the PTV. We consider that the complete radiological response with non-significant related toxicities in this patient could not be possible without a daily CBCT verification system.

6. Conclusions

Daily IGRT with CBCT is a proven method to reduce toxicity and probably increase tumor response due to a better tumor localization and reduction of an interfraction target miss due to anatomical changes. Since progressive anatomical changes are difficult to predict, we recommend frequent on-site image verification over the course of treatment. Special consideration should be made of daily CBCT in patients with pretreatment tumor obstruction, pleural effusions, atelectasis, centrally located, pulmonary embolism, large volume tumors or radiosensitive histology that might resolve early and rapidly during treatment. Since anatomical changes in these

patients are important and might lead to inaccurate radiation dose distribution, or even missing completely the tumor planning target volume, leading to reduced tumor response and increased toxicity. Daily IGRT with CBRT and techniques to control respiratory motion (such as 4DCT and tracking) will improve the results. Further research should be made in how systematic replanning might affect the coverage of microscopic disease since replanning increases uncertainty in this scenario.

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None declared.

Conflict of interest

None declared.

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