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Extra-Corporeal Membrane Oxygenation for Arrested Lung Ablative Radiation Therapy

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Abstract

Objectives: Due to breathing movements, radiotherapy of primary lung cancer requires sophisticated methods to ensure accuracy of the high-precision treatment applied. The aim of this study was to show the use of extra-corporeal membrane oxygenation for ablative radiotherapy while the lung is totally arrested.

Methods: A portable extracorporeal membrane oxygenation device was employed on three separate days without mechanical ventilation to apply stereotactic hypofractionated radiotherapy in three fractions (18 Gy x 3 54 Gy total) to a 68 year old male with a primary tumor (T1N0M0) in the right upper lobe (of the remaining lung). Linear accelerator quality controls (matched isocenter-lasers), patient immobilization monitoring (stereotactic infrared system) and image controls (in cinema mode to observe movements) were made during treatment, and a computed tomography comparison was carried out between pre and post treatment for image verification.

Results: Total extra-corporeal membrane oxygenation time was 270, 283 and 380 minutes for each session respectively. Total administered nominal dose was 54 Gy and it was not necessary to discontinue the treatment since neither lung nor tumor movement was observed during this time. During the second and third treatment days, atelectasis appeared, involving the rear of the lower lobe and it was necessary to increase FiO2 to 0,5. The only post-procedure complication has been a seroma in the groin which was resolved with local wound care.

Conclusion: The described technique of veno-arterial extra-corporeal membrane oxygenation allows the safe arrest of the lung, the immobilization of the tumor and provides enough time for highly accurate ablative radiation therapy.

Keywords: Extracorporeal membrane oxygenation; Arrest mechanical ventilation; Ventilatory arrest; Lung cancer; Radiotherapy

Introduction

Recently, stereotactic body radiation therapy (SBRT) has been established as a curative treatment of lung cancer at early stages in patients who refuse surgery or for those who are medically inoperable [1]. SBRT has emerged as an innovative technique within radiation therapy, to increase accuracy and allow for the delivery of oligo-fractionated ablative doses of radiation [1]. SBRT has been established with high doses of radiation, usually from 12 to 18 Gy per fraction and 3-5 fractions [2]. This type of high-dose external hypo-fractionated ablative radiotherapy has superior efficacy to classical radiation, and it has been suggested as a viable alternative to surgery in early lung cancer [1,3].

SBRT has been shown to reduce relapse rates with low toxicity due to very small margins around the primary tumor [4]. Toxicity increases in proportion to the volume of the tissue treated. In patients with a single lung it is even more important to improve accuracy and reduce the volume to be treated. Multicenter prospective data on SBRT in mostly medically-inoperable patients, are available from several other cooperative groups around the world, and reports show severe late toxicity <5% [1,5]. Prior to SBRT, morphological and functional images are obtained to determine the clinical target volume (CTV) system, since high dose ablative radiotherapy must be provided with high precision and accuracy. This is provided by a stereotactic system and mechanical function of the linear particle accelerator (LINAC) to give a planning tumor volume (PTV) margin as low as possible, to prevent acute and late toxicity [4].

To achieve such high doses of radiation administered extra-cranially, patient immobilization is combined with methods to control tumor and organ motion. Today these methods include synchronization (Gating), persecution (Tracking), patient and technician education in temporary apneas and/or multiple computerized tomography (Cts) including forced spiratory breathing, forced inspiration and free breathing, to define the CTV [6]. At the end of treatment image verification is performed in some centers to ensure that the treatment was highly accurate. During each fraction (1/

alternate day) the patient circuit is as follows: CT room - Linac room - CT room (for image verification).

Respiratory tumor motion during radiotherapy is one of the three main reasons for failure after radiotherapy [7]. In order to improve the accuracy and specificity of the treatment our approach is to arrest lung motion during the whole treatment (planning, processing and testing) by employing extra-corporeal membrana oxygenation (ECMO), which has not been previously reported. Veno-arterial (VA) ECMO or extra-corporeal life support (ECLS) is used as temporary support for the management of life threatening conditions such as heart or heart and lung failure, when no other treatment option is likely to be successful or is used as a bridge to a more permanent supporting device or cardiac transplantation (bridge-to-decision-patient) [8,9]. The ECMO (veno-venous and veno-arterial) technique is also used in specific thoracic surgical procedures and can replace lung ventilation for a few hours to ensure haematosis [10].

In order to achieve complete lung immobility, we considered VA ECMO to be the best option with the added potential benefit of reducing intrathoracic movements.

With this modality of ECMO, another potential benefit is that the heart is also completely drained, reducing effective heart ejection and intrathoracic movements causing bradycardia. Since the patient should be transferred between multiple rooms (from CT to LINAC) and the reverse route for image verification of "immobility", we chose the Cardiohelp® system (Maquet Cardiopulmonary, Hirrlingen, Germany) from among the existing models of portable cardio-pulmonary assistive devices. This is the world's smallest portable heart-lung support system and very suitable for use directly at the patient's bed. It´s also the device of choice for inter-hospital patient transport by ambulance or helicopter [11,12].

The aim of this paper is to describe the first experience of arrested lung ablative radiotherapy which we have named as ALART.

Materials and Methods

Patient

A 68 year old male with criteria for chronic obstructive pulmonary disease (COPD) and emphysema classified as grave GOLD 3 by spirometry test, is the subject case. His history of surgical intervention includes four neoplasms: laryngeal neoplasia (2006), urothelial carcinoma of the bladder (PT2aN0M0), prostate adenocarcinoma with radical prostatectomy and cystectomy (August 2009) and adenocarcinoma of the lung (PT2N0M0) with left pneumonectomy (December 2009). A progressively growing mass was detected, in the last three months, over a scar in right upper lobe (in the remaining lung). Positron Emission Tomography (PET)/CT examination confirmed positive uptake in the lung nodule which was reported as malignant. No other lesions were observed in the extension study, whilst bronchial aspirate cytology was negative. This mass was diagnosed and classified as primary tumor in remaining lung (T1N0M0), however it was not possible to obtain histological confirmation.

Any thoracic surgery and invasive procedure was rejected and instead the patient was proposed for radical radiotherapy. The therapeutic decision was discussed in a multidisciplinary tumor board. Due to the problem of a single deteriorated lung, it was decided that it should be treated with the least invasive procedure possible. The proposed treatment was "compassionate use of hypofractionated radiotherapy" in 3 fractions with 48 h separation.

The procedure was approved by the ethics committee of the hospital and a specific information sheet provided and informed consent obtained.

The preoperative study included CT angiography and Doppler Echo of the ilio-femoral venous system.

Operative technique

The patient was anesthetized on a special trolley for transfers (Imagen Provider® by SIHO, Porriño, Spain) and then immobilized with a vacuum mattress and abdominal compression with damping triangle. Standard antibiotic prophylaxis was used (Cefazolin 1g every 8 hours) and maintained during the three working days. A total intravenous general anesthesia was made with propofol, cisatracurium, fentanyl and remifentanyl with ECG, pulse-oximetry, continuous left radial artery and central venous pressures monitored continuously.

A 1 mg/kg weight heparin bolus was administered before cannulation in each session.

Figure 1: Preparations for starting a fraction radiotherapy. The portable ECMO system with transporting medical air and oxygen cylinders

The Cardiohelp® system was implanted by a peripheral venoarterial cannulation. Since the procedure had to be repeated three times in the same week, percutaneous cannula placement was not employed. A small oblique right groin surgical cut down was used to dissect just one centimeter in the anterior surface of the femoral vein. A small pursestring with 6/0 polypropylene was used to close the hole after cannula removal. After vessel puncture, a guide wire was introduced and located to the right atrium with transesophageal echocardiographic control for a safe placement of the Smartcannula® (36F 630 mm, Smartcanula LLC, Lausanne, Sw) for venous drainage [12].

The arterial return was achieved by "end-to-side" anasthomosis to the right common femoral artery with a 10 mm Fusion Bioline® vascular graft (Maquet Cardiovascular LLC, Wayne, NJ). The cannulae

were safely placed and secured to enable transport from operating room to CT room and from CT to LINAC room.

On the first day, we decided to use a graft length of 12 centimeters. In each work session we discarded 3 centimeters, which we cut at the end of the procedure. The remaining graft was kept folded and empty, and each day the wound was closed, ready for the next day.

Following the launch of ECMO, with the objective of maintaining normothermia and paO_2 within physiological parameters (±120 mmHg), mechanical ventilation was arrested. The patient was then connected to transport ventilator Oxylog 2000 Plus (Dräger, Lübeck, Germany), in continuous positive airway pressure (CPAP) mode with a tidal volume and respiratory rate of 0, and a positive end-expiratory pressure (PEEP) that ranged from 11 to 13 mbar to ensure similar lung inflation volume to spontaneous ventilation of the patient, and keeping the same pressure throughout the process.

As all blood contact surfaces of the ECMO system are heparin coated with the Bioline technique (Maquet Cardiopulmonary AG, Hirrlingen, Germany), systemic anticoagulation can be kept at a minimum. Anticoagulation was monitored by activated clotting time with an objective of between 160 and 180 s. The integrated sensors, which register line pressure, blood temperature, hemoglobin as well as SvO_2, greatly alleviate its management and considerably increase safety [13].

During transportation, power supply was provided by internal batteries and the necessary gas flow for the oxygenator by medical air and oxygen cylinders (Figure 1).

After every radiation therapy session, mechanical ventilation was restarted, circulatory support was disconnected and the vascular cannulae removed, and after a 2-4 hours the patient was extubated without incident.

Radiation therapy

Prescription was hypo-fractionated radiotherapy in three fractions (18 Gy per fraction x three fractions = 54 Gy total).

Computed tomography–guided simulation with contrast was performed in the stereotactic frame. The gross tumor volume (GTV) was delineated on each axial CT slice. The total clinical target volume was the addition of the elastic fusion with the CTV from PET/CT , and an additional 3 mm in the axial plane was added to create the planning target volume (PTV). Three-dimensional treatment planning was used to stereotactically direct a total of 12 coplanar and noncoplanar, nonopposing beams to deliver the planned dose to the PTV. The treatment dose was prescribed to the 80% isodose volume, which covered at least 95% of the PTV.

The LINAC quality controls (match isocenter-lasers), patient immobilization monitoring (stereotactic infrared system) and image controls (cinema mode to observe movements) were made during treatment. CT comparison between pre and post treatment was also made for image verification.

Results

The Cardiohelp pump control data during the three days of treatment are shown in Table 1. No complications related to the ECMO system occurred during device implantation, radiation therapy or during patient transport, whilst limb perfusion was always correct. During the second day of treatment, whilst the patient was in the CT room, blood gas controls from the left radial artery showed oxygen desaturation. Thoracic CT discovered atelectasis involving the posterior third of the lower lobe of the right lung. Bronchoscopy was negative for obstructive secretions. Oxygen desaturation was corrected by increasing pump rate (volume/minute) and enhancing the oxygen alveolar concentration at 0.5 FiO_2 by administration of oxygen from a cylinder and keeping paO_2 at 120 mm Hg.

The atelectasis disappeared the day after, with the patient spontaneously breathing (Figure 2). Although it reappeared in the third treatment session, oxygen desaturation was avoided with the same manouvers (high pump flow and 0.5 FiO_2) as above. Each day, the ECMO device was disconnected without any problems after radiotherapy treatment with image verification, and the cannulae were removed after each session. The patient was admitted to the recovery unit during the total five days of the treatment, was transferred to the ward on the sixth day and was discharged on the eighth day. The patient stayed only three additional days in the hospital after the procedure. The only post-procedure complication has been a seroma in the groin resolved with local wound care.

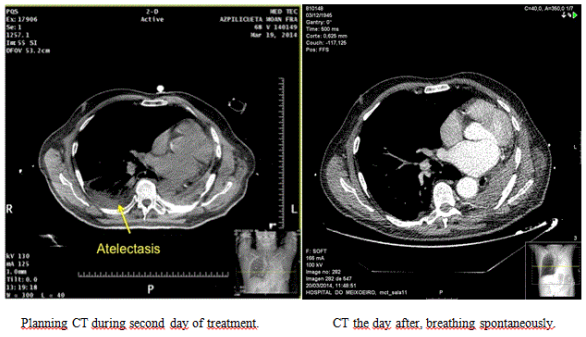

Figure 2: Planning CT during second day of treatment. CT the day after, breathing spontaneously.

Radiation therapy

Arrested lung ablative radiotherapy (ALART) was used in 3 fractions of 18 Gy. The administered nominal dose to PTV was 54 Gy in total and it was not necessary to discontinue the treatment since no lung or tumor movements were observed during this time.

The measured movements indicate movements of equal or less than the accuracy of precision and accuracy systems. There was no observable movement in the eight fields where it was possible to conduct image controls (cinema mode).

During the image verification, a comparison between pre and post-treatment CT in the second session found a difference in tumor position of 2.4 mm left-right, 3 mm cranio-caudal and 2.2 mm antero-posterior. In the third session, the difference was 0.5 mm left-right, 0 mm cranio-caudal, and 0.2 mm antero-posterior, where such differences are no greater than the uncertainties of the voxels (Figure 3 and video 1 Rigid fusion).

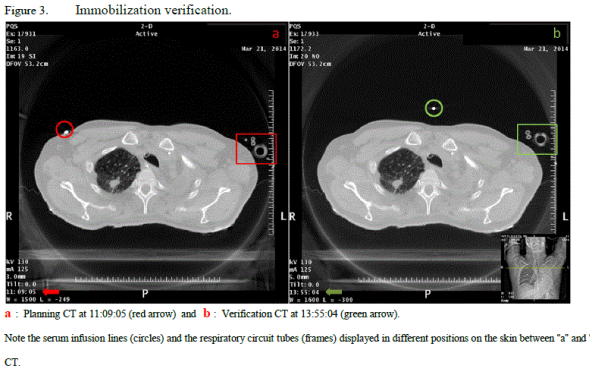

Figure 3: Immobilization verification

After two months follow-up, the patient is doing well and is asymptomatic, and has a control PET/CT scheduled in the next two months.

Discussion

This is a report on the first use of a portable ECMO system with the lung totally arrested for lung ablative radiation therapy (ALART). The aim of this study was to describe the procedure, the result and its potential future applications.

ECMO can be used for total respiratory support. Duration of ventilatory arrest under ECMO can be very long (sometimes several hours). For several years now, ECMO has replaced ventilation during surgical procedures. The first occasion was reported by Horita [14] in 1996 with VV ECMO. Since then, several cases have been described, but data concerning duration of ventilatory arrest with ECMO are scarce in the literature. Korvenoja et al. [15] reported ventilatory arrest lasting 48 min with VV ECMO.

In a recent multi-centre retrospective study, from March 2009 to September 2012 using ECMO for respiratory support during thoracic surgical procedures, it was found that this time could be extended further [10]. The total respiratory support allowed to do the surgery without mechanical ventilation in 28/36 patients (10 trachae, 11 carinae, 2 main bronchi and 5 single-lung surgeries). The median ventilation-off time during ECMO was 78 min with veno-venous (VV) ECMO and 65 min with VA ECMO. Maximal duration was 248 min with VA ECMO. However, the choice between VV ECMO and VA ECMO in replacing ventilation during thoracic surgery depends not only on the necessity of circulatory support but also on centre practices [10].

In order to achieve complete immobility of the lung, our choice was VA ECMO. With the total circulatory support offered by the VA ECMO, it is possible to arrest the lung and also allow for the possibility of inducing bradycardia and thus totally drain the heart with the Smartcannula® [12]. This then decreases the cardiac ejection and thus reduces intrathoracic movements still further. With this described technique, it could also be possible to treat tumors in other organs that move with the diaphragm with greater accuracy.

With a duration time of a few hours of ECMO, there are minimal chances of complications. In our case, ventilation was replaced on the three separate occasions and the time off ventilation duration was 270, 380 and 283 min respectively, with development of partial atelectasis of the lower lobe during the second and third day. Progressive experience will make it possible to substantially reduce the duration of mechanical support.

The possible serious complications of VA ECMO, such as arterial dissection, acute ischaemia of limb, arterial stenosis and brain hypoxaemia [9,10] can be avoided with the described technique. The use of end to side anastomosis of an arterial vascular graft to the common femoral artery for prevention of vascular complications. Also, hypoxaemia observed by atelectasis produced with absence of ventilation can be resolved by reducing cardiac ejection, causing bradycardia and supplying 50% oxygen to keep a PEEP at 13 mbar.

With heparinized circuits, lower heparin doses are required before cannulation and activating clotting time objectives tend to be reduced, thus decreasing risk of haemorrhage.

The use of hand-held Mini-ECMO systems, even 'out-of-centre', was introduced in 2008 [16]. The portable ECMO system plus a continuous fixed lung volume and the patient immobilization methods (vacuum mattress, abdominal compression with damping triangle and special trolley) allows continuous complete lung and patient immobilization during planning, radiation, verification and transfers. Of note, during image verification the estimated deviation was very low, practically negligible in any direction in space and within the uncertainties of imaging systems.

The volume reduction to be irradiated in patients with one single lung and chronic obstructive lung disease is critical. Volume reduction in lung irradiation is mainly intended to prevent pneumonitis and fibrosis [17,18] which is known to be related to radiation dose and volume [19]. With this in mind, a planning tumor volume (PTV) was established here, with a 3 mm margin instead of the usual 5 mm in the axial plane and 10 mm in the longitudinal plane established by most centers [4,20]. So far, with our approach (still more reduced PTV margins), none of the most common symptoms (pain, hemoptysis, cough, etc.) resulting from radiation therapy [21] have appeared, nor have the complications described in the chest wall [22,23].

Although the main limitation of this study is the lack of a long follow-up study to know the final clinical result, at time of submission of the manuscript, the patient was doing very well.

Conclusions

The portable ECMO system with a continuous fixed lung volume and the patient immobilization method allows for the complete immobilization of lung and patient during the entire procedure. The described VA ECMO technique also allows for safe arrest of the lung, inmobilization of the tumor and provides enough time for highly accurate ablative radiation therapy. In our experience, VA ECMO support was a valuable therapeutic help for lung ablative radiotherapy.

This technique of arrested lung ablative radiotherapy (ALART) could be indicated in patients with one remaining lung or with COPD, classified as grave GOLD (3-4).

ALART may lead to the reduction of the PTV margins, with its potential benefits.

Veno-arterial ECMO can provide special conditions (hyperthermia and hyperoxemia) that may be interesting to explore in future clinical trials in radiotherapy

Finally with this described technique it may be possible to treat other tumors in organs that move with the diaphragm with more accuracy. ALART should be considered to increase the indications for SBRT, for special conditions (e.g. liver, adrenal tumors) or patients with loco-regional or general status performance who are unable to tolerate the classical treatments.

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