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A new era of thoracic oncology? Ex-vivo stereotactic ablative radiosurgery within Ex-vivo Lung Treatment System as a hybrid therapy for unresectable locally advanced pulmonary malignancies

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ABSTRACT

The concept of oligometastases is the medical rationale for a local treatment of a limited number of metastatic tumor manifestations. Patients with pulmonary oligometastases are candidates for surgery or radiotherapy, however there are a number of technical issues that limit treatment. Technical issues relating to radiotherapy include organs at risk of irradiation, chest wall toxicity and decreased precision of tumor targeting because of breathing movements. Technical issues relating to surgery include loss of lung parenchyma and unresectability. We propose the hypothesis that ex-vivo radiosurgery as new hybrid technique in thoracic oncology has the capability to overcome these technical issues and will expand the medical spectrum in thoracic oncology. The proposed – highly complex – technique consists of surgical lung explantation, followed by stereotactic radiotherapy during ex-vivo perfusion followed by surgical re-implantation.

1. Introduction

In thoracic oncology, there are many patients presenting with advanced disease not amenable to curative therapy based on conventional concepts. Thus, in case of young and otherwise healthy patients, even very invasive procedures such as ex-vivo therapy of the affected lung subsequent to auto-transplantation, could be taken into consideration (Fig. 1). These considerations refer to both lung cancer patients and patients with lung metastases affecting exclusively the lungs.

The concept of oligometastases is the theoretical rationale for a local treatment of metastatic tumor manifestations. According to this concept, introduced in 1995 by Hellmann and Weichselbaum [1], there is a subpopulation of patients with an intermediate metastatic state. For these patients with up to 5 metastases affecting not more than one or maximally two organs local cancer therapies represent promising treatment options. Recently, the concept of oligometastasis gained new popularity due to the possibility to describe an oligometastatic status based on microRNA expression [2]. It can be assumed that tumor cells leading to an oligometastatic status occur years before tumor cells responsible for diffuse metastases. In this case, due to early detection and an adequate treatment of the malignant tumors, the number of patients with this intermediate metastatic state could increase in the future.

Moreover, for some primary tumors, such as sarcomas or colorectal carcinomas with KRAS-mutation [3], the lung is the solely affected or explicitly preferred target organ of the metastatic process. Recently published data suggest that stereotactic ablative radiotherapy (SABR) – also called stereotactic ablative radiosurgery (SARS) – is a reasonable alternative in two clinical situation. First it is an alternative to surgery in early stage lung cancer [T1-2a (<4 cm; UICC Stage IA-IB], although few patients are diagnosed with early stage lung cancer [4], and secondly to the clinically more common situation of pulmonary metastasectomy [5].

In summary, the therapy of lung malignancies is technically limited. Revolutionary steps in the field of surgery and radiotherapy are necessary to overcome these limitations. In the field of cardiac surgery, a new era had begun with the introduction of less invasive hybrid techniques that combine surgery with catheter based interventions [6]. Why not combine a new lung-preserving surgery technique with simultaneous SARS?

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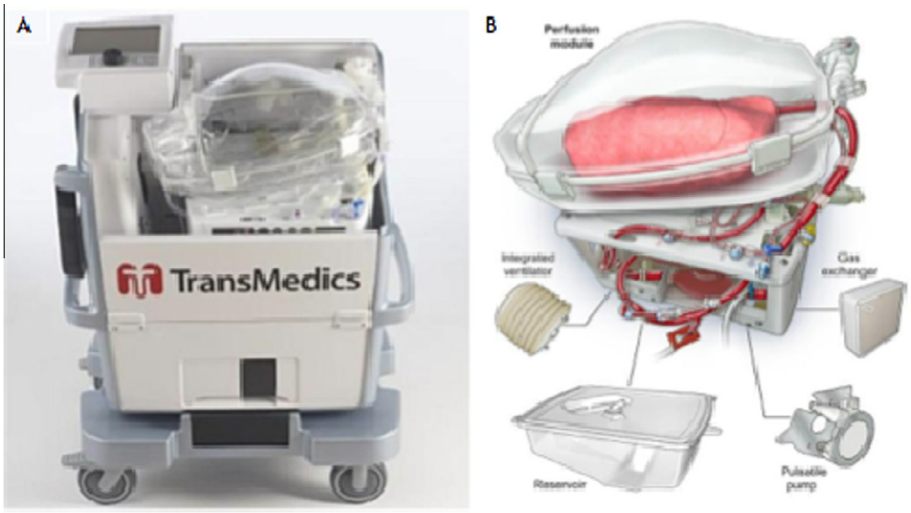

Fig. 1. Organ Care System (A) and schematic view of the perfusion module (B). The photograph shows the device (console with perfusion module in place) with removed cover and control and monitoring unit. The disposable perfusion module integrates the low-resistance polymethylpentene membrane gas exchanger, a pulsatile pump, the fluid reservoir and tubing, an integrated ventilator and an electric perfusate heater. Motors to drive the blood pump and ventilator are installed in the console [10].

2. Hypothesis

We postulate that the introduction of organ preservation hybrid technologies in therapy of lung malignancies consisting of temporary lung explantation and ex-vivo single fraction SARS within the Ex-vivo Lung Treatment System (EvLTS) followed by immediate lung reimplantation will overcome the limiting factors of surgery and radiotherapy, in particular the loss of lung parenchyma by surgical resection and damage to the surrounding organs and tissues by percutaneous radiotherapy, respectively.

2.1. SARS and its technical limitations

Stereotactic ablative radiosurgery is defined as an external beam radiotherapy method to deliver very precisely a high dose radiation to a target within the body, using a single ablative dose to kill all cancer cells within the target. A property of SARS is the very rapid dose fall-off at the target normal tissue interface to avoid damaging of the surrounding normal tissues. However, sparing of normal tissues and organs at risk (OAR, e.g. heart, esophagus, trachea, large vessels, contralateral lung and normal lung tissue) is limited by the fact that the patient is breathing. This leads to movement of the tumor and OARs which increases the irradiated lung volume and decreases precision and sparing of OARs. That limits the applied radiation dose and the efficacy of SARS, because tolerable doses to the lung and OARs located in the mediastinum cannot be exceeded. Several techniques – like respiratory gating – to reduce movement of tumor and OARs are not able to completely eliminate respiration related shifting [7]. The current state of the technique restricts SARS to smaller tumors lying $\geqslant$2 cm beyond the trachea-bronchial tree [8].

One major limitation that cannot be eliminated with any substantial technical progress is the chest wall toxicity (CWT). CWT consists of radiation induced osteonecrotic bone fractures and chronic pain due to soft tissue and/or nerve damage. Furthermore, CWT occurs dose- and volume dependent when the photon rays on their way to the target pass the chest wall and lose a part of their energy there. Most studies have observed that the chest wall volume receiving a dose of $\geqslant$30 Gy (V30) with cut-off values from 30 to 70 cm^3 is the most important parameter predicting chest wall toxicity [9]. Thus, in larger tumors or multiple targets these dose constraints cannot be respected.

In summary, respiratory related movement of the tumor and the OARs, as well as the CWT limit the technical potential of SARS.

2.2. Ex-vivo Lung Treatment System

The EvLTS is a custom made design by the department of Cardiothoracic, Transplantation and Vascular Surgery of Hannover Medical School based on the Organ Care System™ (OCS) Lung, the world's only portable lung perfusion system. The OCS Lung was initially designed for prolonged transport under physiological conditions of explanted human lungs dedicated to allogenic lung transplantation [10]. Similar to a portable heart–lung machine, the OCS allows the precise control and adjustment of ex vivo perfusion and ventilation of the explanted lung with continuous real-time monitoring. The additional feature of the EvLTS, in comparison to the OCS, is the possibility to separate the organ box from the perfusion-, ventilation and control unit witch is indispensable for CT- and MRI imaging. Like the OCS, the EvLTS provides normothermic perfusion and lung parenchyma protective ventilation (Fig. 1). In previous studies we showed that the OCS is a versatile tool for ex-vivo thoracic surgery including lung autotransplantation in pigs as the surgical key step for the intended Ex-vivo stereotactic ablative radiosurgery (unpublished data).

2.3. Hybrid technology of SARS within the EvLTS

A hybrid technology in the areas of thoracic surgery and radiation therapy can be implemented using the EvLTS. The aim is a complete preservation of the lung. Therefore, the human lung is first explanted and then physiologically perfused and ventilated in the EvLTS. This procedure requires no resection of healthy lung tissue. By lung explantation, the CTW as a serious adverse event in SARS of larger lung cancer is thus eliminated. Other thoracic OARs (e.g. esophagus, large vessels, heart) have also become insignificant. The EvLTS provides an artificial "breath hold" which eliminates ventilation induced movements of tumor and surrounding healthy lung parenchyma resulting in a previously impossible real-time differentiation between cancer and normal tissue. The optimal dose distribution to the tumor and sparing of healthy lung tissue provides the opportunity for ablative single fraction radiosurgery of lung malignancies of significant number, any size and