POLMONE:
Altri trattamenti (Immuno-SBTR, Elettroporazione)

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Background

Surgery has always been considered the standard treatment for patients with early-stage lung cancer/mets.

However, non-surgical treatment options have evolved significantly over the past decade with many new and exciting alternative treatments now available.

Extraordinarily complex treatments, those that require tremendous skill or expertise, or those with tremendously high start-up costs may be valuable to those treated, but lose importance if few patients with the condition have the opportunity to receive the treatments.
- Irreversible Electroporation
- SBRT
- Immunotherapy & Locoregional treatments
- Irreversible Electroporation
- SBRT
- Immunotherapy & Locoregional treatments
Electroporation is a new nonthermal ablative technique that is being investigated for the treatment of solid malignancies.

- High-voltage electrical impulses are delivered to tissue in rapid, short intervals (microseconds). The result is disruption of the lipid bilayer of the cell, which creates small pores that allow molecules to enter and leave the cell; if permanent, this leads to cell dysregulation and death.

- Irreversible electroporation results in tissue necrosis presumably due to apoptotic cell death.
Irreversible Electroporation in a Swine Lung Model

Damian E. Dupuy · Bassam Aswad · Thomas Ng

Abstract

Purpose This study was designed to evaluate the safety and tissue effects of IRE in a swine lung model.

Methods This study was approved by the institutional animal care committee. Nine anesthetized domestic swine underwent 15 percutaneous irreversible electroporation (IRE) lesion creations (6 with bipolar and 3 with 3-4 monopolar electrodes) under fluoroscopic guidance and with pancuronium neuromuscular blockade and EKG gating. IRE electrodes were placed into the central and middle third of the right mid and lower lobes in all animals. Postprocedure PA and lateral chest radiographs were obtained to evaluate for pneumothorax. Three animals were sacrificed at 2 weeks and six at 4 weeks. Animals underwent high-resolution CT scanning and PA and lateral radiographs 1 h before sacrifice. The treated lungs were removed en bloc, perfused with formalin, and sectioned.

Gross pathologic and microscopic changes after standard hematoxylin and eosin staining were analyzed within the areas of IRE lesion creation.

Results No significant adverse events were identified. CT showed focal areas of spiculated high density ranging in greatest diameter from 1.1–2.2 cm. On gross inspection of the sectioned lung, focal areas of tan discoloration and increased density were palpated in the areas of IRE. Histological analysis revealed focal areas of diffuse alveolar damage with fibrosis and inflammatory infiltration that respected the boundaries of the interlobular septae. No pathological difference could be discerned between the 2- and 4-week time points. The bronchioles and blood vessels within the areas of IRE were intact and did not show signs of tissue injury.

Conclusion IRE creates focal areas of diffuse alveolar damage without creating damage to the bronchioles or blood vessels. Short-term safety in a swine model appears to be satisfactory.
Irreversible electroporation (IRE) uses direct electrical pulses to create permanent “pores” in cell membranes to cause cell death. In contrast to conventional modalities, IRE has a nonthermal mechanism of action. The objective was to study the histopathological and imaging features of IRE in normal swine lung.

Materials and Methods Eleven female swine were studied for hyperacute (8 h), acute (24 h), subacute (96 h), and chronic (3 week) effects of IRE ablation in lung. Paired IRE applicators were placed under computed tomography (CT) guidance. Some applicators were deliberately positioned near bronchovascular structures. IRE delivery was synchronized with the cardiac rhythm when ablation was performed within 2 cm of the target. Contrast-enhanced CT scan was performed immediately before and after IRE and at 1 and 3 weeks after IRE. Representative tissue was stained with hematoxylin and eosin for histopathology.

Results Twenty-five ablations were created: ten hyperacute, four acute, and three subacute ablations showed edema and necrosis with necrosis of bronchial, alveolar, and vascular epithelium. Bronchovascular architecture was maintained. Chronic ablations showed bronchiolitis obliterans and alveolar interstitial fibrosis. Immediate post-procedure CT images showed linear or patchy density along the applicator tract. At 1 week, there was consolidation that resolved partially or completely by 3 weeks. Pneumothorax requiring chest tube developed in two animals; no significant cardiac arrhythmias were noted.

Conclusion Our preliminary porcine study demonstrates the nonthermal and extracellular matrix sparing mechanism of action of IRE. IRE is a potential alternative to thermal ablative modalities.
Irreversible Electroporation (IRE) Fails to Demonstrate Efficacy in a Prospective Multicenter Phase II Trial on Lung Malignancies: The ALICE Trial

Jens Ricke · Julian H. W. Jürgens · Frederic Deschamps · Lambros Tselikas · Katja Uhde · Ortrud Kosiek · Thierry De Baere

Eligibility criteria included
- primary or secondary lung malignancies,
- normal lung function [forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) [80% normal limits],
- at least 2 cm distance between target lesion and heart, no implants \(\leq 1\) cm to the target lesion,
- no history of epilepsy, cardiac infarction or arrhythmia, no pacemaker,
- a tumor size between 7 and 30 mm.
Results The expected efficacy was not met at interim analysis and the trial was stopped prematurely after inclusion of 23 patients (13/10 between both centers). The predominant tumor entity was colorectal (n = 13). The median tumor diameter was 16 mm (8–27 mm). Pneumothoraces were observed in 11 of 23 patients with chest tubes required in 8 (35%). Frequently observed alveolar hemorrhage never led to significant hemoptysis. 14/23 showed progressive disease (61%). Stable disease was found in 1 (4%), partial remission in 1 (4%) and complete remission in 7 (30%) patients. The relative increase of the current ablation was significantly higher in the group treated successfully as compared to the group presenting local recurrence (p < 0.05). Needle tract seeding was found in three cases (13%).

Conclusions IRE is not effective for the treatment of lung malignancies. We hypothesize that the energy deposition in current IRE probes is highly sensitive to air exposure.
- Irreversible Electroporation

- SBRT
  - Background
  - Results in Lung Tumors
  - SBRT vs Surgery
  - SBRT vs Ablations techniques
  - Guideline

- Immunotherapy & Locoregional treatments
Stereotactic irradiation, first introduced in the context of intracranial stereotactic radiosurgery, is now an established treatment approach for a large variety of cancer presentations throughout the body.

Initially the treatments were called extracranial stereotactic radioablation and later **stereotactic body radiation therapy** (SBRT). More recently, the descriptive term **stereotactic ablative radiotherapy** has come into common use.

The hallmark of SBRT is delivery of a potent, ablative or nearly ablative dose in oligofractions (ie, five or fewer fractions).
Unlike conventional radiotherapy where differential radiation repair between tumor and normal tissue is exploited for a therapeutic advantage, SBRT basically attempts to hit the tumor while ideally altogether avoiding the normal tissue. This is a dramatically different approach than conventional radiotherapy, where large volumes of normal tissues are typically included, even in the high-dose region. The effectiveness of SBRT is attributed primarily to the diminished role of accelerated repopulation due to reduction in overall treatment time, and to its ability to deliver an increased biological effective dose (BED) via large fraction sizes compared to traditional fractionation.

Sroufe & Kong Transl Lung Cancer Res 2015;4(4):438
Reproducible rigid immobilization is necessary, with precise measurement and minimization of set up error.

Strategies should also be applied to control the respiratory motion of tumor and normal tissue during treatment planning and delivery of each fraction.

Treatments are typically delivered in three to five fractions of 10-20 Gy each over a 1-2-week period.

Sroufe & Kong *Transl Lung Cancer Res* 2015;4(4)
Common major toxicities with SBRT are pneumonitis, chest wall/skin injury or rib fracture, pleural effusion, brachial plexopathy, bronchial stenosis, bronchial necrosis with potential for fatal hemoptysis, and esophagitis with potential for stricture, perforation or fistula formation.

The treatment of centrally located tumors, defined as within 2 cm of the proximal bronchial tree, with SBRT has been associated with increased major complications in some trials and is considered somewhat controversial.
Timmerman et al., (2010) JAMA
Multicentre prospective study

- Fifty-five patients with biopsy-proven peripheral T1-T2N0M0 NSCLC (measuring 5 cm in diameter) T1 (n = 44) T2 (n = 11)
- Prescription dose 18 Gy per fraction ×3 fractions (54 Gy total)
- Median follow-up 34.4 months

SBRT is an effective treatment in patients with inoperable NSCLC, with high rates of local tumour control and moderate treatment-related morbidity
Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer.

Sher DJ¹, Wee JO, Punglia RS.

Abstract

Purpose: The standard management of medically inoperable Stage I non-small-cell lung cancer (NSCLC) conventionally has been fractionated three-dimensional conformal radiation therapy (3D-CRT). The relatively poor local control rate and inconvenience associated with this therapy have prompted the development of stereotactic body radiotherapy (SBRT), a technique that delivers very high doses of irradiation typically over 3 to 5 sessions. Radiofrequency ablation (RFA) has also been investigated as a less costly, single-day therapy that thermally ablates small, peripheral tumors. The cost-effectiveness of these three techniques has never been compared.

Methods and Materials: We developed a Markov model to describe health states of 65-year-old men with medically inoperable NSCLC after treatment with 3D-CRT, SBRT, and RFA. Given their frail state, patients were assumed to receive supportive care after recurrence. Utility values, recurrence risks, and costs were adapted from the literature. Sensitivity analyses were performed to model uncertainty in these parameters.

Results: The incremental cost-effectiveness ratio for SBRT over 3D-CRT was $6,000/quality-adjusted life-year, and the incremental cost-effectiveness ratio for SBRT over RFA was $14,100/quality-adjusted life-year. One-way sensitivity analysis showed that the results were robust across a range of tumor sizes, patient utility values, and costs. This result was confirmed with probabilistic sensitivity analyses that varied local control rates and utilities.

Conclusion: In comparison to 3D-CRT and RFA, SBRT was the most cost-effective treatment for medically inoperable NSCLC over a wide range of treatment and disease assumptions. On the basis of efficacy and cost, SBRT should be the primary treatment approach for this disease.
Eligible patients in the STARS and ROSEL studies were those with clinical T1–2 N0 M0, operable NSCLC. Patients were randomly assigned in a 1:1 ratio to SABR or with mediastinal lymph node dissection or sampling. We did a pooled analysis in the pre-treat population using overall survival as the primary endpoint. Both trials are with ClinicalTrials.gov (STARS: NCT00840749; ROSEL: NCT00687986).

Findings—58 patients were enrolled and randomly assigned (31 to SABR and 27 to surgery). Median follow-up was 40.2 months (IQR 23.0–47.3) for the SABR group and 35.4 months (IQR 20.4–40.7) for the surgery group. Six patients in the surgery group died compared with one patient in the SABR group. Estimated overall survival at 3 years was 95% (95% CI 85–100) in the surgery group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0.14 [95% CI 0.01–1.190], log-rank p=0.037). Recurrence-free survival at 3 years was 86% (95% CI 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0.69 [95% CI 0.21–2.29], log-rank p=0.54). In the surgery group, one patient had regional nodal recurrence and two had distant metastases; in the SABR group, one patient had local recurrence, four had regional nodal recurrence, and one had distant metastases. Three (10%) patients in the SABR group had treatment-related adverse events (three [10%] chest wall pain, two [6%] dyspnoea or cough, one [3%] fatigue and rib fracture). No patients given SABR had grade 4 events or treatment-related death. In the surgery group, one (4%) patient died of surgical complications and two patients had grade 3–4 treatment-related adverse events. Grade 3 events occurring in more than one patient in the surgery group were dyspnoea (four [15%] patients), chest pain (four [15%] patients), and lung infections (two [7%]).
Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter

**Interpretation** — SABR could be an option for treating operable stage I NSCLC. Because of small patient sample size and short follow-up, additional randomised studies comparing SABR with surgery in operable patients are warranted.

**Added value of this study**

Both single-arm, phase 2 studies, and retrospective analyses, have shown efficacy and safety of SABR in operable stage I NSCLC. Findings from several non-randomised studies have suggested similar overall survival after either SABR or surgery but were confounded because of potential patient selection bias. Three phase 3 randomised studies comparing the two treatments have failed to complete accrual. Despite its limitations, to our knowledge this analysis is the first and only available randomised evidence comparing SABR with surgery patients who are fit for surgery.

**Implications of all the available evidence**

The results of this combined analysis of STARS and ROSEL suggest that SABR can be considered a treatment option in operable patients needing a lobectomy. The equipoise suggested by our results justifies efforts for additional randomised clinical trials.
Triaging early-stage lung cancer patients into non-surgical pathways: who, when, and what?

Rameses Sroufe¹, Feng-Ming (Spring) Kong²

Table 1 Early-stage NSCLC treatment modality comparison

<table>
<thead>
<tr>
<th>Modality</th>
<th>1-year LC (%)</th>
<th>2-year OS (%)</th>
<th>Common toxicities</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy or sublobar resection</td>
<td>85-95% (1)</td>
<td>80-85% (1)</td>
<td>infection, air leak, myocardial infarction, respiratory failure</td>
<td>severe COPD (FEV1 or DLCO &lt;40% predicted)</td>
</tr>
<tr>
<td>SBRT</td>
<td>80-95%</td>
<td>65-75%</td>
<td>pneumonitis, chest wall pain/rib fracture</td>
<td>central tumors near trachea, mainstem bronchi, hilum, esophagus</td>
</tr>
<tr>
<td></td>
<td>(1,28,30,33)</td>
<td>(1,28,30,33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>60-75% (1,6,7)</td>
<td>60-80% (1,6,7)</td>
<td>pneumothorax, pneumonia, pleural effusion, post-procedure pain</td>
<td>tumors near major blood vessels, esophagus, trachea, mainstem bronchi, or &gt;3 cm</td>
</tr>
<tr>
<td>MWA</td>
<td>67% (10)</td>
<td>75% (10)</td>
<td>pneumothorax, pneumonia, pleural effusion, hemoptyis, post procedure pain</td>
<td>tumors near esophagus, trachea, mainstem bronchi, or &gt;3 cm</td>
</tr>
<tr>
<td>PCT</td>
<td>85-95% (1,13)</td>
<td>~80% (1,13)</td>
<td>pneumothorax, hemorrhage, bronchospasm</td>
<td>tumors &gt;3 cm</td>
</tr>
</tbody>
</table>

Transl Lung Cancer Res 2015;4(4):438-448

The Dark side of the Guidelines – 2nd Interventional Radiologist Under 40 Meeting
POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

Linee Guida AIOM 2017

Carmine Pinto
Presidente Nazionale AIOM

- Riferimento clinico per i PDTA delle sindromi patologie neoplastiche
- Riferimento per le reti oncologiche regionali
- Riferimento per coniugare insieme processi e strategie di cura

The Dark side of the Guidelines – 2° Interventional Radiologist Under 40 Meeting
POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

Linee guida

NEOPLASIE DEL POLMONE

Una accurata valutazione multidisciplinare deve quindi rappresentare il corretto standard terapeutico per qualsiasi paziente affetto da NSCLC in stadio iniziale, con discussione obiettiva di tutte le diverse opzioni a disposizione, e con informazione completa in termini di risultati e morbilità.

Edizione 2016
### Lung cancer Guideline

#### Stadio I, II, IIIA N0-1

<table>
<thead>
<tr>
<th>Qualità dell’evidenza SIGN</th>
<th>Raccomandazione clinica</th>
<th>Forza della raccomandazione clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Nel NSCLC in stadio I, II e IIIA minimo si deve proporre la terapia chirurgica, da eseguirsi esclusivamente presso strutture con elevato volume di attività, da parte di personale specialistico con adeguata esperienza [92-95].</td>
<td>Positiva forte</td>
</tr>
</tbody>
</table>

La SBRT rappresenta certamente il trattamento non chirurgico di scelta per pazienti non operabili affetti da tumori polmonari in stadio iniziale (T1a, T1b, T2a) ed a presentazione periférica [108] (Livello di evidenza: Positivo forte), mentre al momento minori evidenze si hanno per tumori superiori ai 5 cm di diametro ed a localizzazione centrale (a meno di 1-2 cm di distanza dai grossi vasi mediastinici o dall’albero tracheobronchiale).
### Stadio IIIAN2

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Positiva forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Nei pazienti affetti da NSCLC allo stadio cN2 minimo, la condivisione multidisciplinare dell’approccio terapeutico deve essere lo standard. Nell’ambito della valutazione multidisciplinare un trattamento di induzione con doppiette a base di platino seguito da chirurgia, nei pazienti in risposta, è fortemente raccomandato. Il trattamento chirurgico non dovrebbe includere la pneumonectomia ma una lobectomia. Se non fosse possibile una chirurgia minore, alla chemioterapia è opportuno far seguire una radioterapia a scopo curativo [131].</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Nei pazienti in stadio cN2 non minimo (multiple level, bulky), la chemio-radioterapia (concomitante in pazienti adeguatamente selezionati) deve rappresentare lo standard terapeutico [133].</td>
<td></td>
</tr>
</tbody>
</table>
## Table 2: Summary of stereotactic body radiotherapy for pulmonary metastases

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Patients (n) (primary sites)</th>
<th>Meta (n)</th>
<th>Institution</th>
<th>MFU (mo)</th>
<th>Dose (Gy)/</th>
<th>Time (d)</th>
<th>Prescription specification</th>
<th>LC (mo)</th>
<th>OS (mo)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wulf et al[^11]</td>
<td>Retro</td>
<td>CRC (n = 4) others (n = 37)</td>
<td>51</td>
<td>Wuerzburg Univ</td>
<td>30-37/5/3 or 26/1</td>
<td>2-3/interval</td>
<td>-</td>
<td>PTV periphery: 65% isodose of maximum isocenter</td>
<td>80% (24)</td>
<td>33% (2)</td>
<td>N1</td>
</tr>
<tr>
<td>Okunieff et al[^12]</td>
<td>Retro</td>
<td>CRC (n = 14) others (n = 33)</td>
<td>125</td>
<td>Rochester Univ.</td>
<td>Oct-50</td>
<td>1-5 times per week</td>
<td>4-18 (med: 12)</td>
<td>-</td>
<td>91% (24)</td>
<td>38% (24)</td>
<td>G1</td>
</tr>
<tr>
<td>Northias et al[^13]</td>
<td>Retro</td>
<td>CRC (n = 14) others (n = 33)</td>
<td>43</td>
<td>Kyoto Univ.</td>
<td>48-60/4</td>
<td>-</td>
<td>-</td>
<td>PTV periphery: 75%-80% isodose of maximum isocenter</td>
<td>90% (24)</td>
<td>84.3% (24)</td>
<td>G1</td>
</tr>
<tr>
<td>Kim et al[^19]</td>
<td>Retro</td>
<td>CRC (n = 13)</td>
<td>18</td>
<td>Korea Cancer Center</td>
<td>39-51/3</td>
<td>-</td>
<td>-</td>
<td>PTV periphery: 75%-80% isodose of maximum PTV surrounded by 80%-90% isodose PTV</td>
<td>53% (24)</td>
<td>76% (24)</td>
<td>N1</td>
</tr>
<tr>
<td>Rusthoven et al[^24]</td>
<td>P1/II</td>
<td>CRC (n = 9) others (n = 29)</td>
<td>63</td>
<td>multi-institution</td>
<td>48-60/3</td>
<td>&lt; 14</td>
<td>-</td>
<td>PTV periphery: 80%-90% isodose of maximum</td>
<td>96% (24)</td>
<td>39% (24)</td>
<td>G1</td>
</tr>
<tr>
<td>Takeda et al[^26]</td>
<td>Retro</td>
<td>CRC (n = 15) others (n = 19)</td>
<td>125</td>
<td>Ohkama Chuo Hospital</td>
<td>May-50</td>
<td>5</td>
<td>-</td>
<td>PTV periphery: 75%-80% isodose of maximum PTV</td>
<td>72% (24)</td>
<td>-</td>
<td>N1</td>
</tr>
<tr>
<td>Oh et al[^27]</td>
<td>Retro</td>
<td>57</td>
<td>67</td>
<td>Samsung Medical Center</td>
<td>50-60/4-5</td>
<td>-</td>
<td>-</td>
<td>PTV periphery: 75%-80% isodose of maximum</td>
<td>92% (24)</td>
<td>57% (24)</td>
<td>G1</td>
</tr>
<tr>
<td>Ricardi et al[^34]</td>
<td>Retro</td>
<td>CRC, HCC (n = 16) others (n = 51)</td>
<td>77</td>
<td>Giovani Battista Univ</td>
<td>26/1 or 36-45/3</td>
<td>3</td>
<td>PTV periphery: 80% isodose of maximum isocenter</td>
<td>89% (24)</td>
<td>66.5% (24)</td>
<td>G1</td>
<td></td>
</tr>
<tr>
<td>Inoue et al[^37]</td>
<td>Retro</td>
<td>22</td>
<td>31</td>
<td>Hokkaido Univ.</td>
<td>48-49/1</td>
<td>4-7</td>
<td>-</td>
<td>PTV periphery: adapted risk of toxicity</td>
<td>100% (24)</td>
<td>80% (24)</td>
<td>N1</td>
</tr>
<tr>
<td>Widder et al[^21]</td>
<td>Retro</td>
<td>CRC (n = 31) others (n = 11)</td>
<td>≥ 65</td>
<td>Groningen Univ</td>
<td>3/8/1960</td>
<td>-</td>
<td>-</td>
<td>PTV periphery: adapted risk of toxicity</td>
<td>94% (24)</td>
<td>96% (24)</td>
<td>N1</td>
</tr>
<tr>
<td>Inoue et al[^37]</td>
<td>Retro</td>
<td>CRC (n = 37) others (n = 50)</td>
<td>≥ 150</td>
<td>Imitakejima IGRT Clinic</td>
<td>48/4, 52-60/4 or 50/5</td>
<td>4-5</td>
<td>-</td>
<td>PTV periphery: adapted risk of toxicity</td>
<td>80% (24)</td>
<td>47% (24)</td>
<td>G1</td>
</tr>
</tbody>
</table>
**Title:** Results in lung mets

**Abstract:**

**Background:** Lung is the second most common site of colorectal cancer metastasis. Treatment is based mainly on systemic therapy, which has largely evolved lately, but outcome remains relatively poor. The place of locoregional therapies as curative strategies is still debated.

**Purpose:** A systematic literature review was performed by the authors for systemic therapy, surgery, radiofrequency ablation (RFA), and stereotactic body radiation therapy (SBRT). The highest level of evidence for each strategy was presented. Major findings were summarized in a summarized and clinically relevant manner.

**Methods:** All reported studies were descriptive non-comparative reports except for one retrospective study comparing surgery to SBRT. The highest level of evidence for each therapeutic strategy are presented as follows: three large meta-analyses for surgery as well as three prospective trials for RFA and SBRT, respectively.

**Results:** Surgery has the highest level of evidence for cure followed by RFA and SBRT. However, careful patient selection and complete resection of all metastasis are the main principles behind the efficacy of local therapies in the curative setting. Despite promising results, randomized trials are still needed.
11.2 Trattamento chirurgico della malattia avanzata

L’opzione chirurgica è proponibile anche nella malattia avanzata.

In pazienti selezionati ed oligometastatici in sede polmonare o linfonodale, non suscettibili di chirurgia, trovare indicazione un trattamento radioterapico stereotassico (2).

<table>
<thead>
<tr>
<th>Qualità dell’evidenza SIGN</th>
<th>Raccomandazione</th>
<th>Forza della raccomandazione clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>La resezione chirurgica di metastasi polmonari può essere curativa in pazienti selezionati purché i margini di resezione siano negativi. (10)</td>
<td>Positiva forte</td>
</tr>
<tr>
<td>D*</td>
<td>La radioterapia + eventuale chemioterapia può essere utilizzata con intento citoriduttivo o palliativo nei pazienti con sucettibili di chirurgia affetti da recidive pelviche, metastasi linfonodali e polmonari limitate</td>
<td>Positiva debole</td>
</tr>
</tbody>
</table>
13. Novità emergenti

13.1 Immunoterapia

Come in altre neoplasie, anche nei tumori del colon-retto l'immunoterapia rappresenta una nuova frontiera di ricerca.

Una recente pubblicazione (1) ha dimostrato il beneficio di pembrolizumab, un inibitore di PD-1 in 41 pazienti con carcinoma metastatico avanzato, con o senza difetti del 'mismatch repair'. L'immunoterapico è stato somministrato per via endovenosa alla dose di 10 mg/kg di peso corporeo ogni 14 giorni a pazienti con tumori del colon-retto con difetti del 'mismatch repair', a pazienti con tumori del colon-retto senza difetti del 'mismatch repair' e a pazienti con tumori con difetti del 'mismatch repair', ma non del colon-retto. I due co-primary endpoint dello studio erano il tasso di risposta immunitaria obiettiva e il tasso di sopravvivenza libera da progressione immuno-correlata a 20 settimane. Il tasso di risposta immunitaria obiettiva e di sopravvivenza libera da progressione immuno-correlata erano rispettivamente del 40% (4 su 10) e 78% (7 su 9) nei pazienti con tumori del colon-retto con difetti del 'mismatch repair' e dello 0% (0 su 18) e 11% (2 su 18) nei pazienti con tumori del colon-retto senza difetti del 'mismatch repair'. La sopravvivenza mediana libera da progressione e la sopravvivenza globale mediana non sono state raggiunte nella coorte con tumore del colon-retto con difetti del 'mismatch repair', mentre erano rispettivamente di 2.2 e 5.0 mesi nella coorte con tumore del colon-retto senza difetti del 'mismatch repair' (rispettivamente HR di progressione o morte 0.10; p < 0.001; HR di morte 0.22, p = 0.05).
POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

- Irreversible Electoporetion
- SBRT

- Immunotherapy & Locoregional treatments
  - Background: ImmunOncology
  - Background: Immunotherapies & Lung Tumors
  - Immunotherapies & Locoregional Treatments: SBRT
  - Immunotherapies & Locoregional Treatments: RFA/MWA/Cryo
Multiple types of immunotherapy have garnered significant attention recently including dendritic-cell vaccines, T-cell adoptive transfer, and checkpoint blockade immunotherapy (CBI). The significant interest in checkpoint blockade immunotherapy (CBI) stems from the dramatic and durable responses observed in a subset of patients with metastatic disease who have been heavily pre-treated. At its core, CBI functions to inhibit negative regulators of immune responses, or in other words removing the brakes on the immune system. It is now understood that disabling these negative regulators or checkpoints can result in robust and clinically efficacious immune responses which in some cases can control widely metastatic disease.
Background: ImmunOncology

CTLA-4 (Cytotoxic lymphocyte antigen 4) is a receptor present on the surface of cells which binds the co-stimulatory molecules B7-1 and B7-2 on APCs with a much higher affinity than CD28. CTLA-4 is one of the most powerful negative regulatory molecules on the cell surface of T-cells.

Programmed death receptor 1 (PD-1) is a receptor on T-cells which binds PD-L1 PD-L2 and recruits SHP phosphatases to impose a powerful inhibitory signal on T-cell activation and proliferation.

Inhibiting the CTLA-4 and PD-1 pathways using CBI has demonstrated clinical activity in a variety of tumor types including melanoma, lung cancer, renal cancer, bladder cancer, Hodgkin's lymphoma, and prostate cancer.
Il primo studio è stato completato in una sperimentazione svolta in tutto il mondo su 272 pazienti affetti da carcinoma squamoso andati in progressione durante o dopo una prima linea di chemioterapia convenzionale. Nivolumab si è dimostrato superiore a docetaxel, ottenendo una sopravvivenza mediana di 9,7 mesi rispetto a 6 mesi e una riduzione del rischio di morte pari al 41% (HR 0,59). La percentuale di pazienti vivi a un anno era del 42% rispetto al 24% di quelli trattati con docetaxel e la risposta obiettiva era stata pari al 20% per nivolumab, contro il 9% di docetaxel. Il profilo di tossicità è risultato essere nettamente favorevole per nivolumab per i parametri più significativi di tossicità ematologica e gastroenterica e l'efficacia di nivolumab era presente in tutti i sottogruppi dei pazienti trattati, indipendentemente dalle caratteristiche cliniche e dall'espressione di PD-L1.

Il secondo studio (CheckMate -057), presentato all’ASCO nel giugno 2015, era stato formulato in maniera parallela e con la sola differenza che i pazienti arruolati erano affetti da carcinoma del polmone ad istologia non squamosa. In questo caso sono stati trattati a livello mondiale 582 malati in progressione dopo la prima linea di chemioterapia, randomizzati per ricevere nivolumab 3 mg/kg nel gruppo sperimentale vs docetaxel 100 mg/m2 come trattamento convenzionale, con la sopravvivenza obiettivo principale. Lo studio ha registrato un miglioramento della sopravvivenza con nivolumab (12,2 mesi contro 9,4 mesi per docetaxel) e una riduzione del 27% del rischio di morte (HR 0,73). La sopravvivenza ad un anno era pari al 51% nel gruppo trattato con nivolumab, rispetto al 39% del docetaxel e la probabilità di risposta obiettiva è stata uguale al 19% per il nivolumab contro il 12% per il docetaxel.
Harnessing the immunomodulatory effect of thermal and non-thermal ablative therapies for cancer treatment.

Bastianelli C¹, Petrides N²,³, Shah T⁴, Guillaume S¹, Ahmed HU⁵, Arya M¹,⁴.

Abstract
Minimally invasive interventional therapies are evolving rapidly and their use for the treatment of solid tumours is becoming more extensive. The in situ destruction of solid tumours by such therapies is thought to release antigens that can prime an antitumour immune response. In this review, we offer an overview of the current evidence for immune response activation associated with the utilisation of the main thermal and non-thermal ablation therapies currently in use today. This is followed by an assessment of the hypothesised mechanisms behind this immune response priming and by a discussion of potential methods of harnessing this specific response, which may subsequently be applicable in the treatment of cancer patients. References were identified through searches of PubMed/MEDLINE and Cochrane databases to identify peer-reviewed original articles, meta-analyses and reviews. Papers were searched from 1850 until October 2014. Articles were also identified through searches of the authors' files. Only papers published in English were reviewed. Thermal and non-thermal therapies have the potential to stimulate antitumour immunity although the current body of evidence is based mostly on murine trials or small-scale phase 1 human trials. The evidence for this immune-modulatory response is currently the strongest in relation to cryotherapy and radiotherapy, although data is accumulating for related ablative treatments such as high-intensity focused ultrasound, radiofrequency ablation and irreversible electroporation. This effect may be greatly enhanced by combining these therapies with other immunostimulatory interventions. Evidence is emerging into the immunomodulatory effect associated with thermal and non-thermal ablative therapies used in cancer treatment in addition to the mechanism behind this effect and how it may be harnessed for therapeutic use. A potential exists for treatment approaches that combine ablation of the primary tumour with control and possible eradication of persistent, locally recurrent and metastatic disease. However, more work is needed into each of these modalities, initially in further animal studies and then subsequently in large-scale prospective human studies.
Large radiation fields encompassing significant volumes of bone marrow or blood pool have been observed to result in decreases in white blood cell counts, giving rise to the notion that radiation may be generally immunosuppressive.

Nonetheless, with the application of SRS and SBRT there is the possibility of significantly limiting the volume of bone marrow and/or blood pool being irradiated thereby minimizing these potentially consequential immunosuppressive effects.
There is now an established body of pre-clinical literature demonstrating that radiation can modify anti-tumor immune responses:

- **Upregulation of Major Histocompatibility Complex (MHC)** and increase presentation of antigens on surface of tumor cells.
- The **DNA damage and reactive oxygen species** induced by radiation have been shown to result in inflammatory tumor cell death and release of damage associated molecular patterns (DAMPs), which can activate antigen presenting cells.
- **Activation of antigen presenting cells** has also been demonstrated in animal models to enhance tumor antigen cross-presentation in the draining lymph node and result in activation and proliferation of tumor specific cytotoxic cells.
- Radiation has also been shown to **influence expression of cytokines and chemokines**, such as IL-1, IL-2, L-6, TNF-alpha, TGF-beta, CXCL-16, as well as Type I and Type II Interferons which may play a critical role in modulating immune responses.

Given these effects using radiation alone there has been a significant effort to **combine radiation with various immunotherapies** with sometimes striking results within the radiation field (radiosensitizing immunotherapy), as well as distantly outside the radiation field (abscopal responses).
Strategies for combining immunotherapy with radiation for anticancer therapy

Steven N Seyedin¹, Jonathan E Schoenhals², Dean A Lee³, Maria A Cortez², Xiaohong Wang², Sharareh Niknam², Chad Tang¹, David S Hong⁴, Aung Naing⁴, Padmanee Sharma⁵, James P Allison⁵, Joe Y Chang¹, Daniel R Gomez¹, John V Heymach⁶, Ritsuko U Komaki¹, Laurence J Cooper⁷, and James W Welsh¹

Radiation therapy controls local disease but also prompts the release of tumor-associated antigens and stress-related danger signals that primes T cells to promote tumor regression at unirradiated sites known as the abscopal effect. This may be enhanced by blocking inhibitory immune signals that modulate immune activity through a variety of mechanisms. Indeed, abscopal responses have occurred in patients with lung cancer or melanoma when given anti-CTLA4 antibody and radiation. Other approaches involve expanding and reinfusing T or NK cells or engineered T cells to express receptors that target specific tumor peptides. These approaches may be useful for immunocompromised patients receiving radiation. Preclinical and clinical studies are testing both immune checkpoint–based strategies and adoptive immunotherapies with radiation.
08:30-10:00, Auditorium 2 (Barria Room 1)

**Clinical Focus Session**

**Understanding tumour biology**

**Moderators:** P. Gibbs (Melbourne, VIC/AU), N. Goldberg (Jerusalem/IL)

1. Hypoxia and anoxia – friend or enemy?
   - E. Levy (Bethesda, MD/US)

2. IO procedures inducing tumour spread
   - C.T. Sofoceious (New York, NY/US)

3. Post-ablation inflammation and immune reactions – the bad
   - N. Goldberg (Jerusalem/IL)

4. Post-ablation inflammation and immune reactions – the good
   - M.H.M.G.M. den Brok (Nijmegen/NL)

5. Combined locoregional and systemic immunotherapy
   - L. Tselikas (Villejuiff/FR)

10:30-12:00, Auditorium 2 (Barria Room 1)

**Clinical Focus Session**

**Immunotherapy for cancer**

**Moderators:** M. Fuchs (Munich/DE), P. Sarobe (Pamplona/ES)

201.1 Cancer and immune reaction
   - J.J. Lasarte (Pamplona/ES)

201.2 Immunoscore: is it more relevant than TNM?
   - J. Rodríguez (Pamplona/ES)

201.3 Checkpoint inhibitors
   - M. Fuchs (Munich/DE)

201.4 Tumour exosomes – determination of organotropic metastases
   - B. Costa-Silva (Lisbon/PT)

201.5 IO and immunotherapy in cancer
   - J.P. Erinjeri (New York, NY/US)

The Dark side of the Guidelines – 2nd Interventional Radiologist Under 40 Meeting
Focal therapies play an important role in the treatment of cancers where palliation is desired, local control is needed, or surgical resection is not feasible. Pairing immunotherapy with such focal treatments is particularly attractive; however, there is emerging evidence that focal therapy can have a positive or negative impact on the efficacy of immunotherapy. Thermal ablation is an appealing modality to pair with such protocols, as tumors can be rapidly debulked (cell death occurring within minutes to hours), tumor antigens can be released locally, and treatment can be conducted and repeated without the concerns of radiation-based therapies. In a syngeneic model of epithelial cancer, we found that 7 days of immunotherapy (TLR9 agonist and checkpoint blockade), prior to thermal ablation, reduced macrophages and myeloid-derived suppressor cells and enhanced IFN-γ–producing CD8+ T cells, the M1 macrophage fraction, and PD-L1 expressing CD45+ cells. Continued treatment with immunotherapy alone or with immunotherapy combined with ablation (primed ablation) then resulted in a complete response in 80% of treated mice on day 90, and primed ablation expanded CD8+ T cells as compared with all control groups. When the tumor burden was increased by implantation of 3 orthotopic tumors, successive primed ablation of 2 discrete lesions resulted in survival of 60% of treated mice as compared with 25% of mice treated with immunotherapy alone. Alternatively, when immunotherapy was begun immediately after thermal ablation, the abscopal effect was diminished and none of the mice within the group exhibited a complete response. In summary, we found that immunotherapy begun before ablation can be curative and can enhance efficacy in the presence of a high tumor burden. Two mechanisms have potential to impact the efficacy of immunotherapy when begun immediately after the ablation: mechanical changes in the tumor microenvironment and inflammatory-mediated changes in immune phenotype.
PD-1 blockade boosts radiofrequency ablation-elicited adaptive immune responses against tumor

Liangrong Shi#1,2,3, Lujun Chen#1,3, Changping Wu1,2,3,* Yibei Zhu4, Bin Xu1,3, Xiao Zheng1,3, Mingfen Sun1,3, Wen Wen4, Xichao Dai1,2,3, Min Yang1,2,3,4, Quansheng Lv4, Binfeng Lu5,* and Jingting Jiang1,3,*

Radiofrequency ablation (RFA) has been shown to elicit tumor-specific T cell responses but is not sufficient to prevent cancer progression. Here we investigated suppressive mechanisms limiting the efficacy of RFA.

**Material design**—We performed a retrospective case-controlled study on patients with colorectal cancer liver metastases who had received primary tumor resection with or without RFA for liver metastases. Tumor infiltrating T cells and tumoral PD-L1 in human colorectal cancer tissues were analyzed by immunohistochemistry. T cell responses and PD-1/PD-L1 expression were also characterized in a RFA mouse model. In the combined effect of RAF and PD-1 blockade was evaluated in the mouse RFA model.

—We found that RFA treatment of liver metastases increased not only T cell infiltration and PD-L1 expression in primary human colorectal tumors. Using mouse tumor models, we demonstrated that RFA treatment of one tumor initially enhanced a strong T cell-mediated immune response in tumor. Nevertheless, tumor quickly overcame the immune response by inhibiting the function of CD8+ and CD4+ T cells, driving a shift to higher Treg to Teff ratio and up-regulating of PD-L1/PD-1 expression. Furthermore, we established that the combination of RFA and anti-PD-1 antibodies significantly enhanced T cell immune responses, resulted in stronger antitumor immunity and prolonged survival.

**Conclusions**—The PD-L1/PD-1 axis plays a critical role in dampening RFA-induced immune responses. And this study provides a strong rationale for combining RFA and PD-1 blockade in the clinical setting.
CONCLUSIONS

- SBRT has credibility because it has been initiated and accepted by the general radiation oncology community, both academic and private practice.

- The use of SBRT in the community is becoming widespread because of availability of technologies, knowledge and practice-based training, and acceptance of clinical results.

- IRE **NOT raccomanded**

- New frontiers: Immunotherapies and Immunotherapies + Locoregional Treatments (SBRT +++)

- Need Multidisciplinary approach and Randomized Studies
Save the Date

3rd Edition

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