The dark side of the guidelines
2nd Interventional Radiologist under 40 Meeting
Interventional Oncology
8-10 Maggio 2017
Bologna
Società Medica Chirurgica - Palazzo dell'Archiginnasio

POLMONE:
Altri trattamenti (Immuno-SBTR, Elettroporazione)

Chiara Floridi

Diagnostic and Interventional Radiology
Fatebenefratelli Hospital
Milan, Italy

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 Electoporation
- SBRT
- Immunotherapy & Locoregional treatments

- Irreversible Electoporation
- SBRT
- Immunotherapy & Locoregional treatments

versible Electoporation

- 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.

versible Electoporation

Cardiovasc Intervent Radiol (2011) 34:391–395
DOI 10.1007/s00270-010-0091-9

LABORATORY INVESTIGATION

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.

versible Electoporation

Cardiovasc Intervent Radiol (2011) 34:1278–1287
DOI 10.1007/s00270-011-0143-9

LABORATORY INVESTIGATION

Percutaneous Irreversible Electroporation Lung Ablation: Preliminary Results in a Porcine Model

Ajita Deodhar · Sébastien Monette · Gordon W. Single Jr · William C. Hamilton Jr · Raymond H. Thornton · Constantinos T. Sofocleous · Majid Maybody · Stephen B. Solomon

act

tive Irreversible electroporation (IRE) uses direct ical pulses to create permanent "pores" in cell ranes to cause cell death. In contrast to conventional ities, IRE has a nonthermal mechanism of action. bjective was to study the histopathological and ng features of IRE in normal swine lung.

ials and Methods Eleven female swine were stud- r hyperacute (8 h), acute (24 h), subacute (96 h), and ic (3 week) effects of IRE ablation in lung. Paired lar IRE applicators were placed under computed graphy (CT) guidance. Some applicators were delib- y positioned near bronchovascular structures. IRE delivery was synchronized with the cardiac rhythm when ablation was performed within 2 cm of the Contrast-enhanced CT scan was performed imme- y before and after IRE and at 1 and 3 weeks after IRE on. Representative tissue was stained with hematox- nd eosin for histopathology.

ts Twenty-five ablations were created: ten hyper- four acute, and three subacute ablations showed ar edema and necrosis with necrosis of bronchial, hiolar, 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.

versible Electoporation

Cardiovasc Intervent Radiol (2015) 38:401–408
DOI 10.1007/s00270-014-1049-0

CLINICAL INVESTIGATION INTERVENTIONAL ON

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

act

se To assess safety and efficacy of irreversible poration (IRE) of lung malignancies.

ials and Methods Patients with primary and sec- lung malignancies and preserved lung function ncluded in this prospective single arm trial. Primary secondary endpoints were safety and efficacy. tment goal was 36 subjects in 2 centers. Patients went IRE under general anesthesia with probe nent performed in Fluoroscopy-CT. The IRE system yed was NanoKnife® (Angiodynamics). System s for the ablation procedure followed the manufac- recommendations. The Mann–Whitney *U* test was o evaluate the correlation of nine technical parame- with local tumor control. Median follow up was nths.

Eligibility criteria included

- primary or secondary lung malignancies,
- normal lung function [forced expiratory volume in second (FEV1) and forced vital capacity (FVC) [8 normal limits],
- at least 2 cm distance between target lesion and no implants \1 cm to the target lesion,
- no history of epilepsia, cardiac infarction or arrhyt no pacemaker,
- a tumor size between 7 and 30 mm.

versible Electoporation

sults The expected efficacy was not met at interim lysis and the trial was stopped prematurely after lusion of 23 patients (13/10 between both centers). The ninant tumor entity was colorectal ($n = 13$). The med- tumor diameter was 16 mm (8–27 mm). Pneumotho- es were observed in 11 of 23 patients with chest tubes uired in 8 (35 %). Frequently observed alveolar hem- nage never led to significant hemoptysis. 14/23 showed gressive disease (61 %). Stable disease was found in 1 %), partial remission in 1 (4 %) and complete remission 7 (30 %) patients. The relative increase of the current ing ablation was significantly higher in the group trea- successfully as compared to the group presenting local urrence ($p < 0.05$). Needle tract seeding was found in ee cases (13 %).

nclusions IRE is not effective for the treatment of lung lignancies. We hypothesize that the energy deposition h current IRE probes is highly sensitive to air exposure

Cardiovasc Intervent Radiol (2015) 38:401–408
DOI 10.1007/s00270-014-1049-0

CLINICAL INVESTIGATION INTERVENTIONAL ON

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

- Irreversible Electoporetion

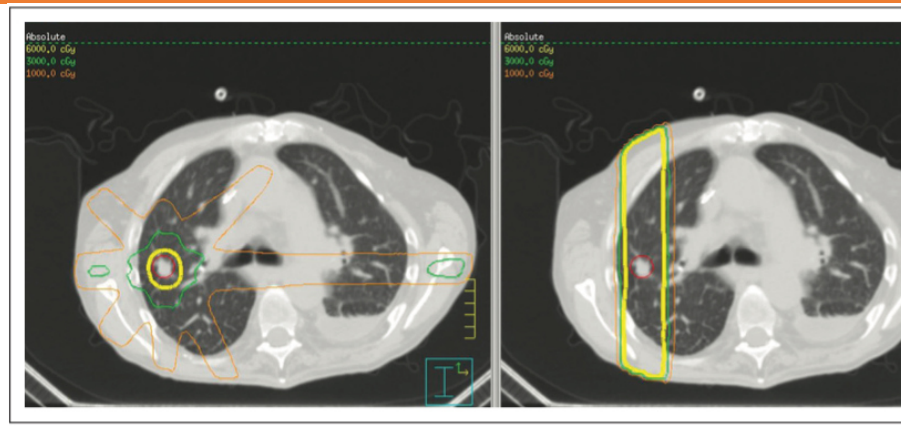
- SBRT
  - ✓ Background
  - ✓ Results in Lung Tumors
  - ✓ SBRT vs Surgery
  - ✓ SBRT vs Ablations techniques
  - ✓ Guideline

- Immunotherapy & Locoregional treatments

SBRT: Background

- 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**).

SBRT: Background



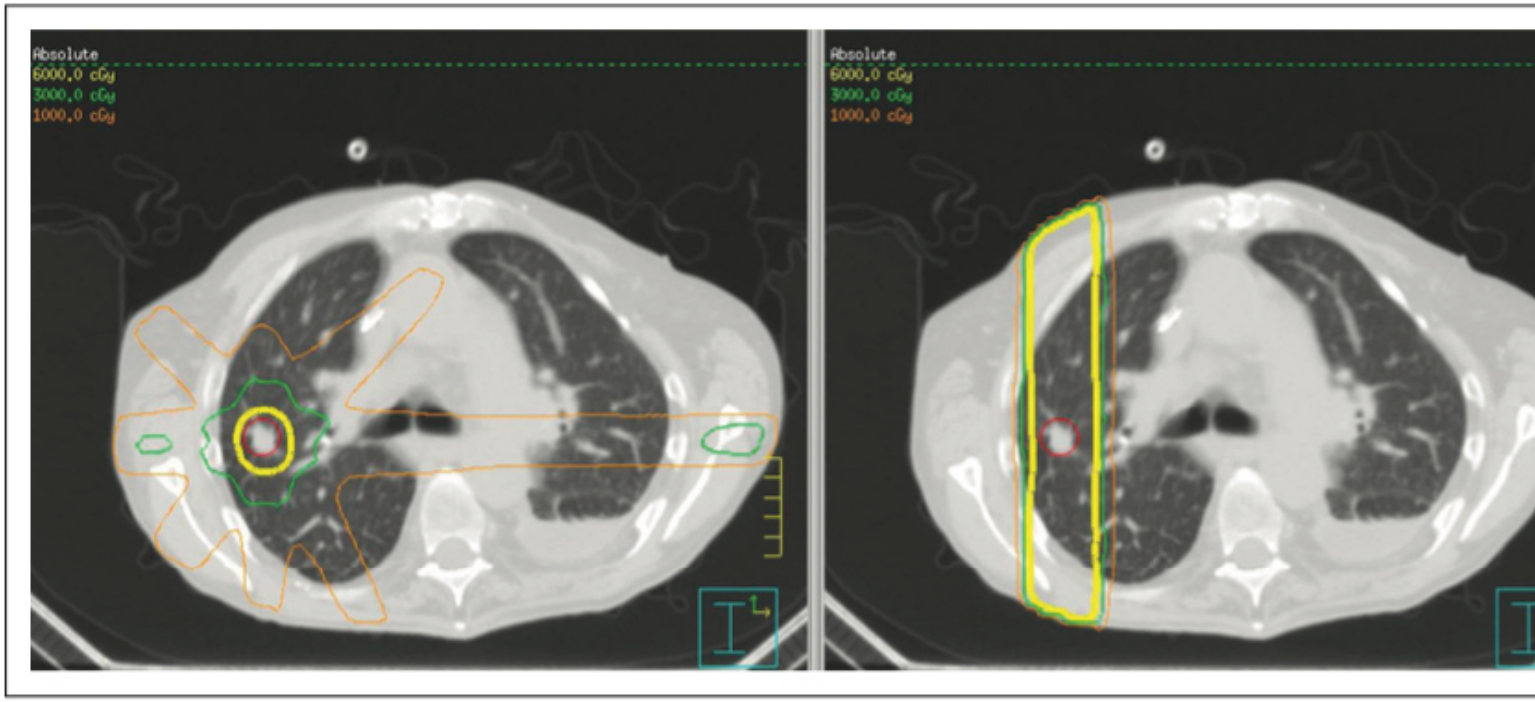
Unlike conventional radiotherapy where differential radiation repair between tumor ar
normal tissue is exploited for a therapeutic advantage, SBRT basically attempts to hit th
tumor while ideally altogether avoiding the normal tissue.

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 a increased biological effective dose (BED) via large fraction sizes compared to traditio fractionation**

Sroufe & Kong *Transl Lung Cancer Res* 2015;4(

SBRT: Background



- 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(

SBRT: Background

- 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.

Sroufe & Kong *Transl Lung Cancer Res* 2015;4(

T: Results in lung cancer

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

Median overall survival	48.1 m
Overall 3-year survival	55.8%
Disseminated recurrence at 3 years	22.1%
3-year primary tumour control rate	97.6%
Local-regional control rate	87.2%
DFS	48.3%
Adverse events:	
Grade 3	7/55 (1
Grade 4	2/55 (3

- SBRT is an effective treatment in patients with inoperable NSCLC, with high rates of local tumour control and moderate treatment-related morbidity

SBRT vs Ablation

Int J Radiat Oncol Biol Phys. 2011 Dec 1;81(5):e767-74. doi: 10.1016/j.ijrobp.2010.10.074. Epub 2011 Feb 6.

Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer.

Sher DJ[1], 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.

SBRT vs Surgery

col. 2015 June ; 16(6): 630–637. doi:10.1016/S1470-2045(15)70168-3.

actic ablative radiotherapy versus lobectomy for e stage I non-small-cell lung cancer: a pooled analysis of domised trials

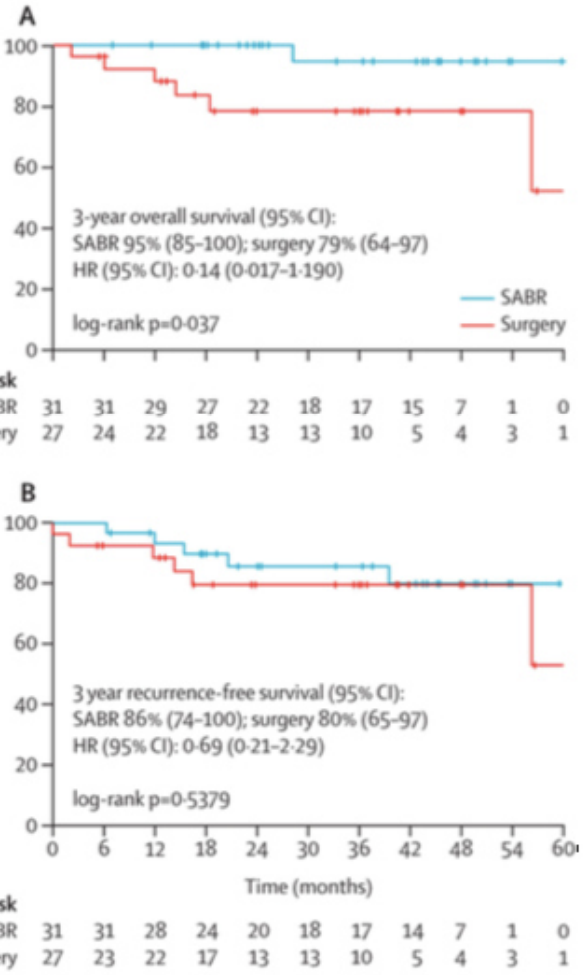
ng*, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter

—Eligible patients in the STARS and ROSEL studies were those with clinical T1–2a 0M0, 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 o-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 su Median follow-up was 40.2 months (IQR 23.0–47.3) for the SABR group and 35.4 mon 40.7) for the surgery group. Six patients in the surgery group died compared with one pa the SABR group. Estimated overall survival at 3 years was 95% (95% CI 85–100) in the group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0.14 [95% C 1.190], log-rank p=0.037). Recurrence-free survival at 3 years was 86% (95% CI 74–10 SABR group and 80% (65–97) in the surgery group (HR 0.69 [95% CI 0.21–2.29], log- p=0.54). In the surgery group, one patient had regional nodal recurrence and two had dis metastases; in the SABR group, one patient had local recurrence, four had regional noda recurrence, and one had distant metastases. Three (10%) patients in the SABR group ha treatment-related adverse events (three [10%] chest wall pain, two [6%] dyspnoea or co one [3%] fatigue and rib fracture). No patients given SABR had grade 4 events or treatm related death. In the surgery group, one (4%) patient died of surgical complications and patients had grade 3–4 treatment-related adverse events. Grade 3 events occurring in mo one patient in the surgery group were dyspnoea (four [15%] patients), chest pain (four [patients), and lung infections (two [7%]).

POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

SBRT vs Surgery



ed and five had recurrence in the SABR group compared with six and six ctively, in the surgery group. SABR=stereotactic ablative radiotherapy.

Lancet Oncol. 2015 June ; 16(6): 630–637. doi:10.1016/S1470-2045(15)70168-3.

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 o small patient sample size and short follow-up, additional randomised studies comparing SAB 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.

SBRT vs Ablation

Triaging early-stage lung cancer patients into non-surg pathways: who, when, and what?

Rameses Sroufe[1], Feng-Ming (Spring) Kong[2]

Transl Lung Cancer Res 2015;4(4):438-44

Table 1 Early-stage NSCLC treatment modality comparison

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

ung Tumor Guideline

ndardizzare sulla base dell'evidenza "la pratica ica" e insieme essere "strumento" di **formazione aggiornamento**

orire l'uniformità, la condivisione e la **tidisciplinarietà** delle strategie di cura

antire al paziente sull'intera territorio nazionale la sibilità di accesso alla "**migliore cura**"

ndere disponibile linee guida elaborate con una odologia validata per le **istituzioni nazionali e ionali, per gli organismi regolatori ed i "payers"**

Linee Guida AIOM 2017

Carmine Pinto
Presidente Nazionale AIOM

- Riferimento clinico per i PDTA delle si patologie neoplastiche
- Riferimento per le reti oncologiche regiona
- Riferimento per coniugare insieme proce strategie di cura

Disponibile su App Store

Aiom Linee Guida

Disponibile su Google play

POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

ung Tumor Guideline

[redacted]		Oncologia Medica – Ospedale Santa Maria della Misericordia – AO di Perugia
[redacted]		Oncologia Medica – Ospedale Santa Maria della Misericordia – AO di Perugia
[redacted]		Oncologia Medica – ASL 2 – Lucca
[redacted]		Chirurgia Toracica – Ospedale Sacro Cuore Don Calabria – Negrar (VR)
[redacted]		Oncologia Medica – AUSL Romagna – Ravenna
[redacted]		Pneumologia – AOU Ospedali Riuniti – Ancona
[redacted]		Oncologia Medica – Ospedale Sacro Cuore Don Calabria – Negrar (VR)
[redacted]		Dipartimento di Oncologia – Università di Torino – AOU San Luigi Gonzaga - Orbassano (TO)
[redacted]		Chirurgia Toracica – Ospedale Santa Maria della Misericordia – Università di Perugia
[redacted]		Dipartimento di Oncologia, S.C. Radioterapia – AOU Città della Salute e della Scienza – Torino
[redacted]		Oncologia Medica – AO S. Giuseppe Moscati – Avellino
[redacted]		Oncologia Medica – AOU Policlinico S. Orsola Malpighi – Bologna
[redacted]	AIPO	Pneumologia ad indirizzo Oncologico AORN dei Colli – Napoli
[redacted]	SICT	Chirurgia Toracica – Policlinico Gemelli – Università Cattolica del Sacro Cuore – Roma
[redacted]	SIAPEC	Anatomia Patologica – AORN A. Cardarelli – Napoli
[redacted]	SIAPEC	Anatomia Patologica – AOU Policlinico di Modena
[redacted]		Dipartimento di Oncologia – Università di Torino - AOU San Luigi Gonzaga – Orbassano (TO)

Aiom
Associazione Italiana di Oncologia Medica

Linee guida

NEOPLASIE DEL POLMONE

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

Edizione 2016

POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

: Lung cancer Guideline

Stadio I, II, IIIAN0-1

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
C	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].	**Positiva forte**

i di operabilità sono triplici: operabilità biologica (prospettiva di radicalità in relazione allo stadio); ilità anatomica (minor volume di resezione necessario ad ottenere la radicalità); operabilità funzionale ità respiratoria predetta dopo intervento radicale utile a garantire una sufficiente funzionalità toria).

Nei pazienti non operabili per motivi internistici e/o di funzionalità respiratoria, si ricorre, quando possibile, alla radioterapia. Risultati migliori rispetto alla radioterapia convenzionale in termini di controllo locale e sopravvivenza sono oggi ottenibili con la radioterapia stereotassica (SBRT: *Stereotactic Body Radiation Therapy*, o SABR: *Stereotactic Ablative Radiotherapy*), per quanto un recente studio randomizzato scandinavo (SPACE) abbia dimostrato una superiorità della SBRT rispetto alla radioterapia conformazionale 70 Gy/35 frazioni solo in termini di minor tossicità (esofagea e polmonare), e non in termini di miglior *outcome* clinico [107].

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 periferica [108] (**Livello di evidenza: Positivo forte**), mentre al momento minori evidenze si hanno per tumori superiori ai 5 cm di diametro od a localizzazione centrale (a meno di 1-2 cm di distanza dai grossi vasi mediastinici o dall'albero tracheo-bronchiale).

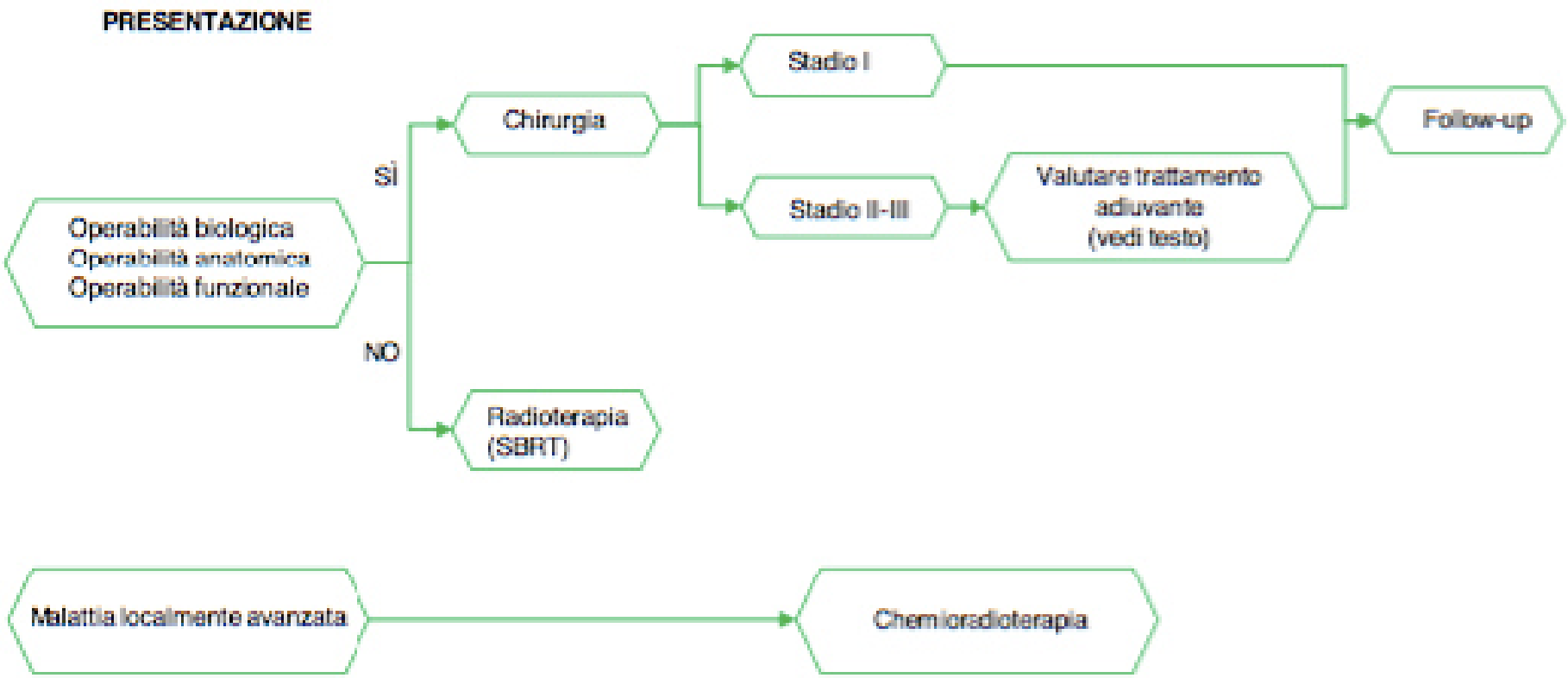
A DELLA RACCOMANDAZIONE CLINICA

ccomandazione clinica viene graduata in base all'importanza clinica, su 4 livelli:

one	Terminologia	Significato
e	"Nei pazienti con (criteri di selezione) l'intervento xxx **dovrebbe** essere preso inconsiderazione come opzione terapeutica di prima intenzione"	L'intervento in esame dovrebbe essere considerato come prima opzione terapeutica (evidenza che i benefici sono prevalenti sui danni)
le	"Nei pazienti con (criteri di selezione) l'intervento xxx **può** essere preso in considerazione come opzione terapeutica di prima intenzione, in alternativa a yyy"	L'intervento in esame può essere considerato come opzione di prima intenzione, consapevoli dell'esistenza di alternative ugualmente proponibili (incertezza riguardo alla prevalenza dei benefici sui danni)

: Lung cancer Guideline

Figura 2: NSCLC: malattia non metastatica



: Lung cancer Guideline

Stadio IIIAN2

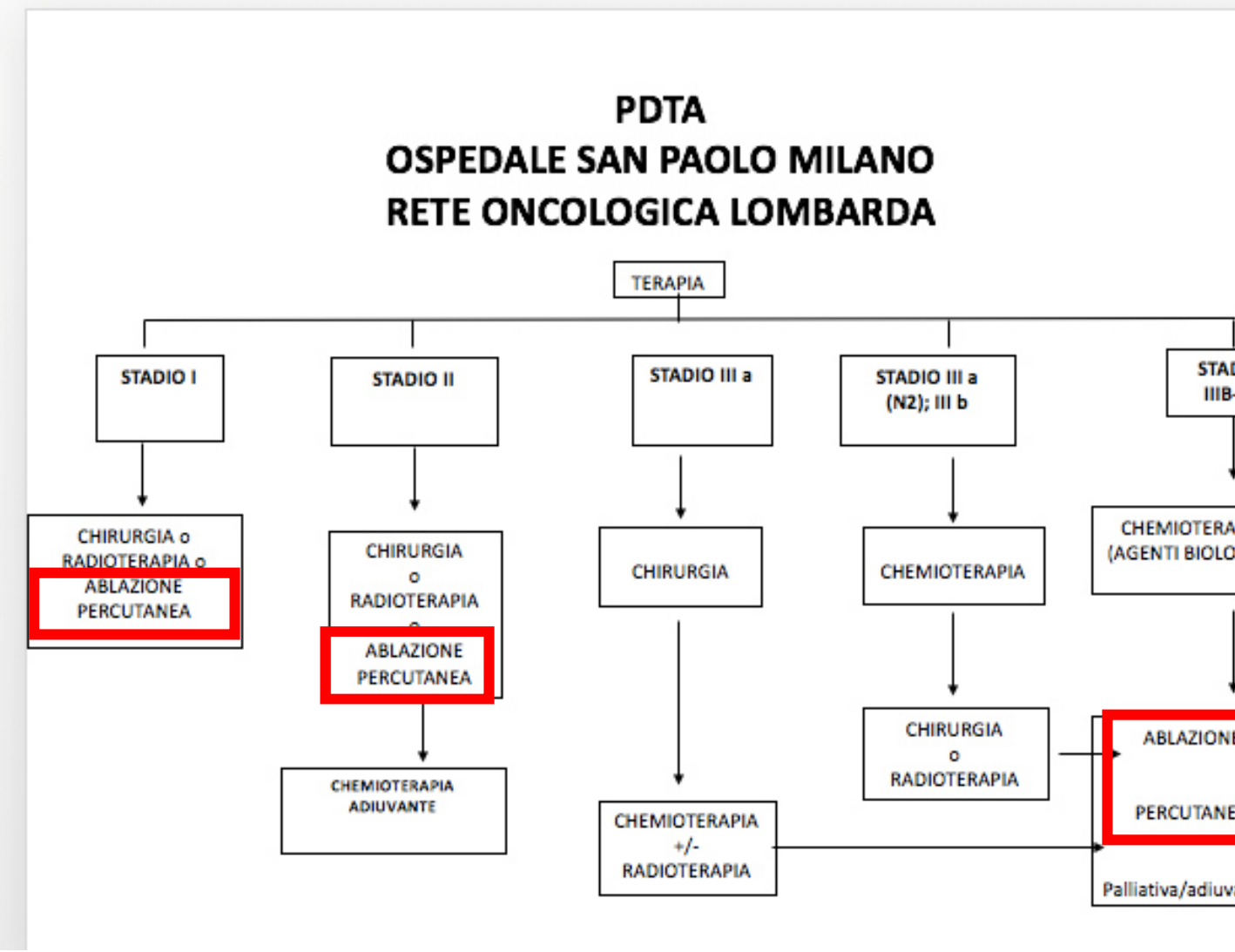
A	Nei pazienti affetti da NSCLC allo stadio cN2 minimo, la condivisione multidisciplinare dell'approccio terapeutico deve essere lo standard. Nell'ambito della valutazione multidisciplinare un trattamento di induzione con doppiette a base di platino seguito da chirurgia, nei pazienti in risposta, è fortemente 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].	**Positiva forte**
A	Nei pazienti in stadio cN2 non minimo (multiple level, bulky), la chemio-radioterapia (concomitante in pazienti adeguatamente selezionati) deve rappresentare lo standard terapeutico [133].	**Positiva forte**

: Lung cancer Guideline

Rete Oncologica Lombarda

Linee Guida AIOM e Reti Oncologiche Regionali

- ranzia della qualità/standard assistenziali
- ropriatezza diagnostica e terapeutica
- zionalizzazione dei servizi
- egrazione dei PDTA
- zionalizzazione delle risorse e tecnologie
- mizzazione della spesa
- lementazione della ricerca



T: Results in lung mets

TOPIC HIGHLIGHT

niversary Special Issues (5): Colorectal cancer

stereotactic body radiotherapy for oligometastasis lorectal cancer

a, Naoko Sanuki, Etsuo Kunieda

Gastroenterol 2014 April 21; 20(15): 4220-4229

Table 2 Summary of stereotactic body radiotherapy for pulmonary metastasis

Ref.	Study	Patients (*n*) (primary sites)	Meta (*n*)	Institution	MFU (mo)	Dose (Gy)/	Time (d)	Prescription specification	LC (mo)	OS (mo)	Toxi
Wulf *et al*[70]	Retro	CRC (*n* = 4) others (*n* = 37)	51	Wuerzburg Univ	10	30-37.5/3 or 26/1	2-3 interval	PTV periphery: 65% isodose of maximum	80% (24)	33% (24)	N
Okunieff *et al*[71]	Retro	CRC (*n* = 14) others (*n* = 35)	125	Rochester Univ.	19	Oct-50	1-5 times per week	Isocenter	91% (24)	38% (24)	G
Norihisa *et al*[72]	Retro	CRC (*n* = 14) others (*n* = 35)	43	Kyoto Univ.	27	48-60/4	4-18 (med: 12)	Isocenter	90% (24)	84.3% (24)	G
Kim *et al*[73]	Retro	CRC (*n* = 13)	18	Korea Cancer Center	28	39-51/3	3	PTV periphery: 75%-80% isodose of maximum	53% (24)	76% (24)	N
Rusthoven *et al*[74]	P I/II	CRC (*n* = 9) others (*n* = 29)	63	multi-institution	15	48-60/3	< 14	Isocenter, PTV surrounded by 80%-90% isodose	96% (24)	39% (24)	G
Takeda *et al*[44]	Retro	CRC (*n* = 15) others (*n* = 19)	CRC (*n* = 21) others (*n* = 23)	Ofuna Chuo Hospital	29 15	May-50	5	PTV periphery: 75%-80% isodose of maximum	72% (24) 94% (24)	- -	N
Oh *et al*[75]	Retro	57	67 CRC, HCC (*n* = 16) others (*n* = 51)	Samsung Medical Center	21	50-60/4-5	-	PTV periphery: 75%-80% isodose of maximum	92% (24) 81% (24) 100% (24)	57% (24)	G
Ricardi *et al*[76]	Retro	61	77	Giovanni Battista Univ	20	26/1 or 36-45/3	3	PTV periphery:	89% (24)	66.5% (24)	G
Inoue *et al*[77]	Retro	22	31	Hokkaido Univ.	25	Apr-48	4-7	80% isodose of maximum isocenter	100% (24)	80% (24)	N
Widder *et al*[78]	Retro	CRC (*n* = 31) others (*n* = 11)	⩾ 65	Groningen Univ	43	3/8/1960	-	PTV periphery: adapted risk of toxicity	94% (24)	86% (24)	-
Inoue *et al*[79]	Retro	CRC (*n* = 37) others (*n* = 50)	⩾ 150	Miyakojima IGRT Clinic	15	48/4, 52-60/4 or 50/5	4-5	-	80% (24)	47% (24)	G G

T: Results in lung mets

ntest Cancer. 2016 Sep;47(3):223-31. doi: 10.1007/s12029-016-9818-4.

emic Versus Local Therapies for Colorectal Cancer Pulmonary Metastasis: What to Choose and n?

T[1], Tselikas L[2], Yazbeck C[3], Kattan J[4].

nor information

ct

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

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

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

SSION: Surgery has the highest level of evidence for cure followed by RFA and SBRT. However, careful patient selection and te resection of all metastasis are the main principles behind the efficacy of local therapies in the curative setting. Despite aging results, randomized trials are still needed.

T: Lung Mets Guideline

Aiom
Associazione Italiana di Oncologia Medica

Edizione 2016

Linee guida

RI DEL COLON RETTO

o Beretta		Oncologia Medica - Humanitas Gavazzeni - Bergamo
vatore		Oncologia Medica - Azienda Ospedaliero - Università Integrata di Verona - Verona
e Aprile		Oncologia - Azienda Ospedaliero Universitaria S. Maria Misericordia - Udine
gildo		Oncologia Medica - Azienda Ospedaliera Papa Giovanni XXIII - Bergamo
chele		Oncologia - ASL 5 Liguria - La Spezia
rmaehi		Oncologia Medica - Humanitas Cancer Center - Rozzano (MI)
o Cosimelli		Chirurgia Oncologica - Ist. Naz. Tumori Regina Elena - Roma
Maiello		Oncologia - Ospedale Casa Sollievo Sofferenza IRCCS - S.Giovanni Rotondo (FG)
Normanno		Biologia Cellulare e Bioterapie - INT-Fondazione Pascale - Napoli
Sciallero		Oncologia Medica 1 - Azienda Ospedaliera S.Martino IRCCS - IST - Genova
ca Valvo		Radioterapia 1 - Fondazione Istituto Tumori - Milano
o Cancian	SIMG	ULSS7 - Conegliano Veneto (TV)
Cannizzaro	AIGO	Gastroenterologia - C.R.O. - Aviano (PN)
o De Paoli	AIRO	Radioterapia - C.R.O. - Aviano (PN)
co Di Costanzo		Oncologia Medica - Azienda Ospedaliero Universitaria Careggi - Firenze
Falcone		Oncologia Medica - Azienda Ospedaliero Universitaria Pisana - Pisa
Labianca		Oncologia - Azienda Ospedaliero Giovanni XXIII - Bergamo
i Lanza	SIAPEC	Anatomia Patologica - Arcispedale S. Anna - Azienda Ospedaliero Universitaria - Ferrara
		Chirurgia Clinica 1 - Università - Padova
Risio	SIAPEC	Anatomia Patologica Istituto per la Ricerca e la Cura del Cancro IRCC Candiolo TO
co Tonelli	SICO	Chirurgia - Università degli Studi di Firenze - Firenze
o Valentini		Gemelli ART – Fondazione "Policlinico A. Gemelli" - Roma
Zaniboni		Oncologia - Fondazione Poliambulatorio - Brescia

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).

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
D	La resezione chirurgica di metastasi polmonari può essere curativa in pazienti selezionati purché i margini di resezione siano negativi. (10)	**Positiva forte**
D*	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	**Positiva debole**

*Op

T: Lung Mets Guideline

13. Novita' emergenti

13.1 Immunoterapia

Come in altre neoplasie, anche nei tumori del colon-retto l'immonoterapia 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, $p = 0.05$).

- Irreversible Electoporetion

- SBRT

- Immunotherapy & Locoregional treatments
  - Background: ImmunOncology
  - Background: Immunotherapies & Lung Tumors
  - Immunotherapies & Locoregional Treatments: SBRT
  - Immunotherapies & Locoregional Treatments: RFA/MWA/Cryo

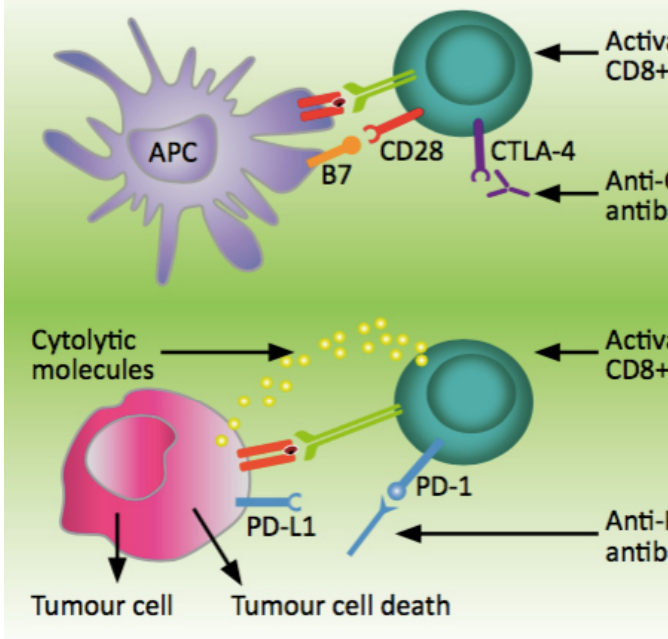
ground: ImmunOncology

- 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 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.

ground: ImmunOncology

TLA-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 uch higher affinity than CD28. CTLA-4 is one of the most powerful negative gulatory molecules on the cell surface of T-cells.

ogrammed 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 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

unotherapies & Lung Tumors

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 9.2 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 a nel giugno 2015, era stato formulato in maniera parallela e con la sola differenza che i pazienti arruolati erano affetti d carcinoma del polmone ad istologia non squamosa. In que sono stati trattati a livello mondiale 582 malati in progressi dopo la prima linea di chemioterapia, randomizzati per ric nivolumab 3 mg/ kg nel gruppo sperimentale vs docetaxel m2 come trattamento convenzionale, con la sopravvivenza obiettivo principale. Lo studio ha registrato un miglioramen della sopravvivenza con nivolumab (12,2 mesi contro 9,4 m docetaxel) e una riduzione del 27% del rischio di morte (HR La sopravvivenza ad un anno era pari al 51% nel gruppo tra nivolumab, rispetto al 39% del docetaxel e la probabilità di obiettiva è stata uguale al 19% per il nivolumab contro il 1 docetaxel.

Immunotherapies & ocoRegional treatments

Tumour Biol. 2015 Dec;36(12):9137-46. doi: 10.1007/s13277-015-4126-3. Epub 2015 Sep 30.

Harnessing the immunomodulatory effect of thermal and non-thermal ablative therapies for cancer treatment.

Bastianpillai C[1], Petrides N[2,3], Shah T[1], Guillaumier S[1], Ahmed HU[1], Arya M[1,4].

Abstract

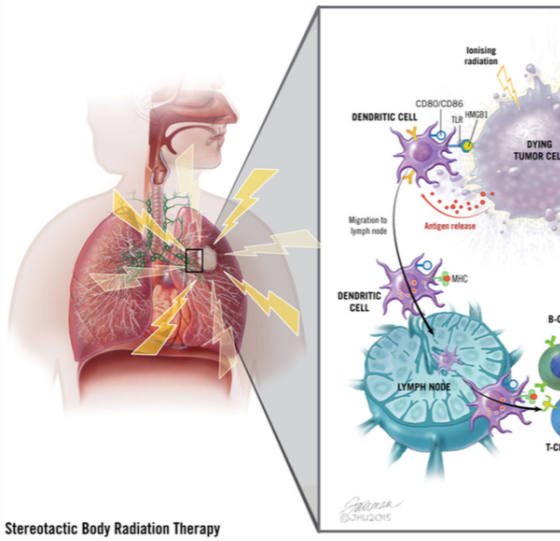
Minimally invasive interventional therapies are evolving rapidly and their use for the treatment of solid tumours is becoming more extensive. The in situ destruction of solid tumours by such therapies is thought to release antigens that can prime an antitumour immune response. In this review, we offer 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.

Immunotherapies & SBRT

ology (Williston Park). 2015 May ; 29(5): 331–340.

reotactic Radiotherapy combined with Immunotherapy:
gmenting Radiation's Role in Local and Systemic Treatment

ew B. Sharabi[1], Phuoc T. Tran[1,2,3], Michael Lim[1,3,4], Charles G. Drake[2,3], and Theodore Weese[1,2,3]



- 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.

POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

Immunotherapies & SBRT

e is now an established body of pre-clinical literature demonstrating that radiation can modify anti-tumor immune
nses:

- **Upregulation of Major Histocompatibility Complex** (MHC) and increase presentation of antigens on surface of t 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 cytotox 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 mmunotherapies** with sometimes striking results within the radiation field (radiosensitizing immunotherapy), as well distantly outside the radiation field (abscopal responses).

Immunotherapies & SBRT

Immunotherapy. 2015 ; 7(9): 967–980. doi:10.2217/imt.15.65.

Strategies for combining immunotherapy with radiation for anticancer therapy

Steven N Seyedin[#1], Jonathan E Schoenhals[#2], Dean A Lee[3], Maria A Cortez[2], Xiaohong Wang[2], Sharareh Niknam[2], Chad Tang[1], David S Hong[4], Aung Naing[4], Padmanee Sharma[5], James P Allison[5], Joe Y Chang[1], Daniel R Gomez[1], John V Heymach[6], Ritsuko U Komaki[1], Laurence J Cooper[7], and James W Welsh[*,1]

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.

POLMONE: Altri trattamenti (Immuno-SBRT, Elettroporazione)

Immunotherapies & RFA/MWA/Cryo

ECIO 2017

April 23-26
Bilbao, Spain

08:30-10:00, Auditorium 2 (Barria Room 1)
Clinical Focus Session
802 Understanding tumour biology

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

2.1 Hypoxia and anoxia – friend or enemy?
E. Levy (Bethesda, MD/US)
2.2 IO procedures inducing tumour spread
C.T. Sofocleous (New York, NY/US)
2.3 Post-ablation inflammation and immune reactions – the bad
N. Goldberg (Jerusalem/IL)
2.4 Post-ablation inflammation and immune reactions – the good
M.H.M.G.M. den Brok (Nijmegen/NL)
2.5 Combined locoregional and systemic immunotherapy
L. Tselikas (Villejuif/FR)

10:30-12:00, Auditorium 2 (Barria Room 1)
Clinical Focus Session
CF 201 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)

Immunotherapies & RFA/MWA/Cryo

ing is key to effective incorporation nage-guided thermal ablation into unotherapy protocols

. Silvestrini,[1] Elizabeth S. Ingham,[1] Lisa M. Mahakian,[1] Azadeh Kheirolomoom,[1] Yu Liu,[1]
e,[1] Sarah M. Tam,[1] Samantha T. Tucci,[1] Katherine D. Watson,[1] Andrew W. Wong,[1]
onjazeb,[2] Neil E. Hubbard,[3] William J. Murphy,[4] Alexander D. Borowsky,[3]
rine W. Ferrara[1]

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 the can have a positive or negative impact on the efficacy of immunotherapy. Thermal ablation an appealing modality to pair with such protocols, as tumors can be rapidly debulked (cell de occurring within minutes to hours), tumor antigens can be released locally, and treatment ca be conducted and repeated without the concerns of radiation-based therapies. In a syngenei model of epithelial cancer, we found that 7 days of immunotherapy (TLR9 agonist and check blockade), prior to thermal ablation, reduced macrophages and myeloid-derived suppressor and enhanced IFN-γ–producing $CD8^+$ T cells, the M1 macrophage fraction, and PD-L1 express $CD45^+$ cells. Continued treatment with immunotherapy alone or with immunotherapy combi with ablation (primed ablation) then resulted in a complete response in 80% of treated mice day 90, and primed ablation expanded $CD8^+$ T cells as compared with all control groups. Whe tumor burden was increased by implantation of 3 orthotopic tumors, successive primed abla of 2 discrete lesions resulted in survival of 60% of treated mice as compared with 25% of mi treated with immunotherapy alone. Alternatively, when immunotherapy was begun immedi after thermal ablation, the abscopal effect was diminished and none of the mice within the exhibited a complete response. In summary, we found that immunotherapy begun before ab can be curative and can enhance efficacy in the presence of a high tumor burden. Two mecha have potential to impact the efficacy of immunotherapy when begun immediately after ther ablation: mechanical changes in the tumor microenvironment and inflammatory-mediated in immune phenotype.

Immunotherapies & RFA/MWA/Cryo

Clin Cancer Res. 2016 March 1; 22(5): 1173–1184. doi:10.1158/1078-0432.CCR-15-1352.

PD-1 blockade boosts radiofrequency ablation-elicited adaptive immune responses against tumor

Liangrong Shi[#1,2,3], **Lujun Chen**[#1,3], **Changping Wu**[1,2,3,*], **Yibei Zhu**[4], **Bin Xu**[1,3], **Xiao Zheng**[1,3], **Mingfen Sun**[1,3], **Wen Wen**[4], **Xichao Dai**[1,2,3], **Min Yang**[1,2,3,4], **Quansheng Lv**[4], **Binfeng Lu**[5,*], and **Jingting Jiang**[1,3,*]

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

ental design—We performed a retrospective case-controlled study on patients with us colorectal cancer liver metastases who had received primary tumor resection with or e-operative RFA for liver metastases. Tumor infiltrating T cells and tumoral PD-L1 in human colorectal cancer tissues were analyzed by immunohistochemistry. T cell sponses and PD-1/PD-L1 expression were also characterized in a RFA mouse model. In he 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 D-L1 expression in primary human colorectal tumors. Using mouse tumor models, we ted that RFA treatment of one tumor initially enhanced a strong T cell-mediated immune response in tumor. Nevertheless, tumor quickly overcame the immune respons inhibiting the function of $CD8^+$ and $CD4^+$T cells, driving a shift to higher Treg to Teff up-regulating of PD-L1/PD-1 expression. Furthermore, we established that the combin of RFA and anti-PD-1 antibodies significantly enhanced T cell immune responses, resu stronger antitumor immunity and prolonged survival.

Conclusions—The PD-L1/PD-1 axis plays a critical role in dampening RFA-induce 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: Immonotherapies and Immunotherapies + Locoregional Treatments (SBRT +++)
- Need Multidisciplinary approach and Randomized Studies

3rd EDITION

ICIO

Italian Conference on
Interventional Oncology

METASTASES

Honorary Presidents
Gian Paolo Cornalba (Milano/IT)
Antonio Rotondo (Napoli/IT)

Presidents
Luca Brunese (Campobasso/IT)
Maurizio Cariati (Milano/IT)
Gianpaolo Carrafiello (Milano/IT)

Scientific Secretariat
Chiara Floridi (Milano/IT)
Anna Maria Ierardi (Milano/IT)

Local Scientific Committee
Salvatore Alessio Angileri (Milano/IT)
Nicola Flor (Milano/IT)
Giuseppe Franceschelli (Milano/IT)
Alberto Magenta Biasina (Milano/IT)
Umberto Rossi (Milano/IT)
Andrea Sacrini (Milano/IT)
Marco Zaffaroni (Milano/IT)

December
12-13
2017
icio2017.com

ASSIMPREDIL ANCE
via San Maurilio 21
Milano