RESPONSABILI SCIENTIFICI
ANNA CECILIA BETTINI
LUCIA BONOMI
CARLO ALBERTO TONDINI

DOCENTI
ANNA CECILIA BETTINI
LUCIA BONOMI
GIUSEPPE CIARAVINO
DAVIDE CROCE
FABIANO DI MARCO
ANDREA GIANATTI
ALESSANDRO LUCIANETTI
ROBERTO NANI
FABIO PICCOLI
FRANCESCO TARANTINI
CARLO ALBERTO TONDINI

PROVIDER ECM E SEGRETERIA ORGANIZZATIVA

over group
via Pagliari, 4 - 26100 Cremona
tel 0372 23310 - fax 0372 569605
info@overgroup.eu - www.overgroup.eu

CREDITI ECM
Il corso ha ottenuto 4 crediti ECM per Biologo, Infermiere, Medico Chirurgo specializzato in Oncologia, Chirurgia Generale, Chirurgia Toracica, Pneumologia, Radiologia, Anatomia patologica, Radioterapia

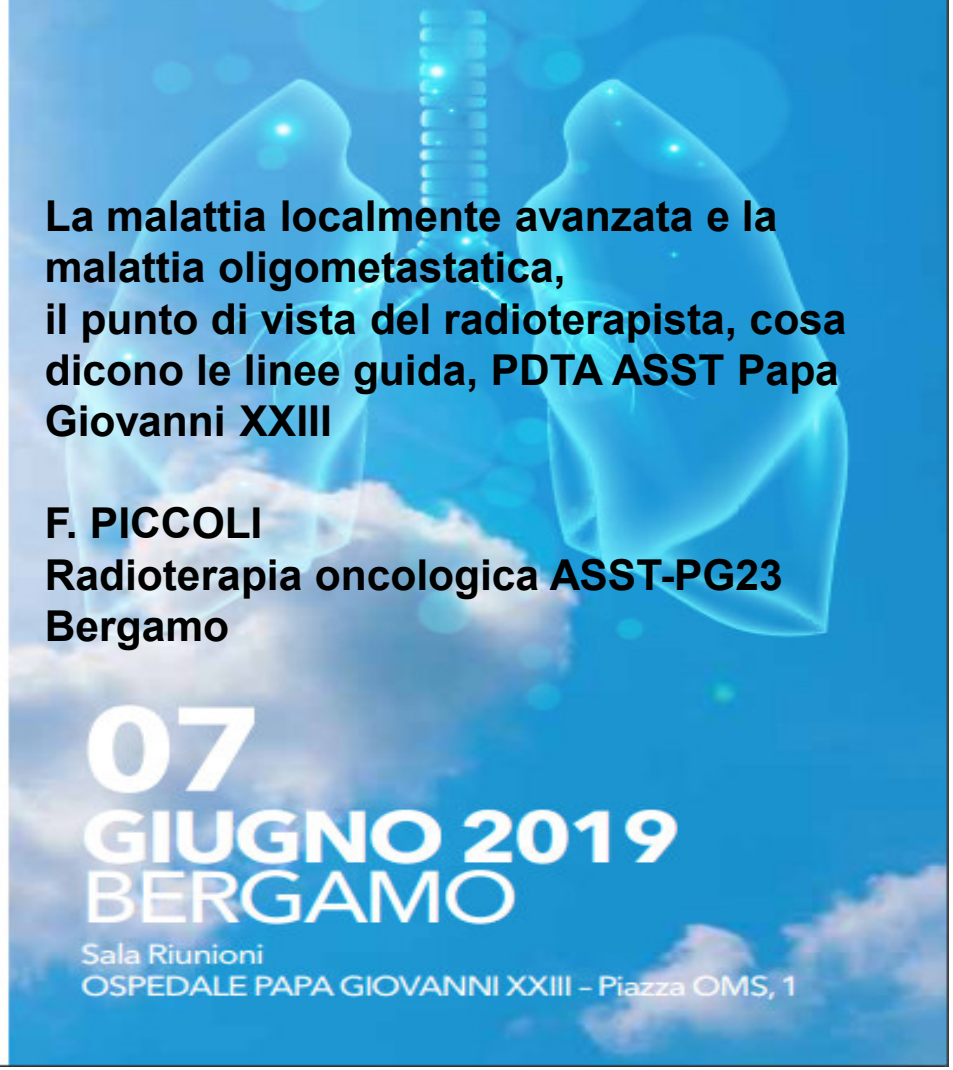
OBIETTIVO FORMATIVO
LINEE GUIDA – PROTOCOLLI – PROCEDURE

CON LA SPONSORIZZAZIONE NON CONDIZIONANTE DI

Roche

AGGIORNAMENTO SULLE NEOPLASIE TORACICHE:

COSA DICONO LE LINEE GUIDA, LA REALTÀ AL PAPA GIOVANNI XXIII, PROSPETTIVE FUTURE



La malattia localmente avanzata e la malattia oligometastatica, il punto di vista del radioterapista, cosa dicono le linee guida, PDTA ASST Papa Giovanni XXIII

F. PICCOLI
Radioterapia oncologica ASST-PG23 Bergamo

07 GIUGNO 2019
BERGAMO

Sala Riunioni
OSPEDALE PAPA GIOVANNI XXIII – Piazza OMS, 1

Annals of Oncology 26: 1573–1588, 2015
doi:10.1093/annonc/mdv187
Published online 20 April 2015

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

W. E. E. Eberhardt[1], D. De Ruysscher[2], W. Weder[3], C. Le Péchoux[4], P. De Leyn[5], H. Hoffmann[6], V. Westeel[7], R. Stahel[8], E. Felip[9], S. Peters[10] & Panel Members[†]

[1]Department of Medical Oncology, West German Cancer Centre, University Hospital, University Duisburg-Essen, Ruhrlandklinik, Essen, Germany; [2]Department of Radiation Oncology, KU Leuven–University of Leuven, University Hospitals Leuven, Leuven, Belgium; [3]Division of Thoracic Surgery, University Hospital Zürich, Zürich, Switzerland; [4]Department of Radiation Oncology, Gustave Roussy Cancer Institute, Villejuif, France; [5]Department of Thoracic Surgery, University Hospitals, KU Leuven, Leuven, Belgium; [6]Department of Thoracic Surgery, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; [7]Department of Chest Disease, University Hospital, Besançon, France; [8]Clinic of Oncology, University Hospital Zürich, Zürich, Switzerland; [9]Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [10]Département d'Oncologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Received 6 August 2014; revised 24 March 2015; accepted 9 April 2015

To complement the existing treatment guidelines for all tumour types, ESMO organises consensus conferences to focus on specific issues in each type of tumour. The 2nd ESMO Consensus Conference on Lung Cancer was held on 11–12 May 2013 in Lugano. A total of 35 experts met to address several questions on non-small-cell lung cancer (NSCLC) in each of four areas: pathology and molecular biomarkers, first-line/second and further lines of treatment in advanced disease, early-stage disease and locally advanced disease. For each question, recommendations were made including reference to the grade of recommendation and level of evidence. This consensus paper focuses on locally advanced disease.
Key words: non-small-cell lung cancer, locally advanced, stage III, recommendations, ESMO

What is the optimal radiation regimen given to stage III NSCLC patients?

Dose and fractionation in concurrent chemoradiotherapy Recommendation 6.1.1: **60–66 Gy in 30–33 daily** fractions is recommended for concurrent chemoradiotherapy [I, A].
Maximum overall treatment time should not exceed seven weeks [III, B].
'Biological intensification', such as treatment acceleration, is not standard practice in concurrent chemoradiotherapy schedules [III, B]. The majority of clinical concurrent chemoradiotherapy regimen

Dose and fractionation in sequential chemoradiotherap

Recommendation 6.1.2: Promising outcome is achieved with accelerated radiotherapy [I, A]. A potential radiation schedule could be the delivery of **66 Gy in 24 fractions [II, C].**

Radiation doses in the preoperative setting

Recommendation 6.1.3: Standard preoperative radiation doses within chemoradiotherapy protocols should be **between 40 and 50 Gy in conventional fractionation or 40–45 Gy in accelerated fractionation (bid application) [I, B]**

Radiotherapy technique

Recommendation 6.3: Quality assurance and **dose constraints** are required as a prerequisite [I, A].

Elective mediastinal nodal irradiation Recommendation 6.2: Elective mediastinal nodal irradiation— prophylactic Reirradiation of non-involved mediastinal nodes—is not recommended [I, B]. **Prophylactic irradiation of non-involved mediastinal nodes—is not recommended [I, B**

Radiotherapy costraints

POLMONI UNITI V20 of 30-35% or and MLD value of 13 Gy

MIDOLLO SPINALE DMAX < 46 Gy

ESOFAGO dose media < 34 Gy, V35 < 50%, V50 < 40%, V70 < 20%

CUORE V25 < 10 % , V30 < 46%

Definition of the GTV after chemotherapy

Table 2 Phase III clinical studies which had in one of arms radiotherapy delivered after induction chemotherapy and recommended the use of pre-chemotherapy volumes for target definition

Trial, year	Design of the study
Le Chevalier et al. 1991	Radiotherapy alone versus sequential radiochemotherapy
Dillman et al. 1996	Radiotherapy alone versus sequential radiochemotherapy
Furuse et al. 1999	Sequential radiochemotherapy versus concurrent radiochemotherapy
Sause et al. 2000	Radiotherapy alone versus sequential radiochemotherapy
Curran et al. 2003	Sequential radiochemotherapy versus concurrent radiochemotherapy
Zatloukal et al. 2004	Sequential radiochemotherapy versus concurrent radiochemotherapy
Fournel et al. 2005	Sequential radiochemotherapy versus concurrent radiochemotherapy
Huber et al. 2006	Induction chemotherapy followed by radiotherapy or concurrent radiochemotherapy
Vokes et al. 2007	Concurrent radiochemotherapy versus induction chemotherapy followed by concurrent radiochemotherapy
van Meerbeeck et al. 2007	Induction chemotherapy followed by surgery or definitive radiotherapy
Belderbos et al. 2007	Sequential radiochemotherapy versus concurrent radiochemotherapy
Thomas et al. 2008	Induction chemotherapy followed by radiochemotherapy and surgery versus surgery and postoperative radiotherapy

Use the prechemotherapy volumes for target definition.

Target volume definition in non small lung cancer. Jeremicet all, advances in radiation oncology in lung cancer, Springer-Verlag 2011

Radiother Oncol. 2018 Apr;127(1):1-5. doi: 10.1016/j.radonc.2018.02.023. Epub 2018 Mar 28.

ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer.

Nestle U[1], De Ruysscher D[2], Ricardi U[3], Geets X[4], Belderbos J[5], Pöttgen C[6], Dziadiuszko R[7], Peeters S[8], Lievens Y[9], Hurkmans C[10], Slotman B[11], Ramella S[12], Faivre-Finn C[13], McDonald F[14], Manapov F[15], Putora PM[16], LePéchoux C[17], Van Houtte P[18].

⊕ Author information

Abstract

Radiotherapy (RT) plays a major role in the curative treatment of locally advanced non-small cell lung cancer (NSCLC). Therefore, the ACROP committee was asked by the ESTRO to provide recommendations on target volume delineation for standard clinical scenarios in definitive (chemo)radiotherapy (RT) and adjuvant RT for locally advanced NSCLC. The guidelines given here are a result of the evaluation of a structured questionnaire followed by a consensus discussion, voting and writing procedure within the committee. Hence, we provide advice for methods and time-points of diagnostics and imaging before the start of treatment planning and for the mandatory and optional imaging to be used for planning itself. Concerning target volumes, recommendations are given for GTV delineation of primary tumour and lymph nodes followed by issues related to the delineation of CTVs for definitive and adjuvant radiotherapy. In the context of PTV delineation, recommendations about the management of geometric uncertainties and target motion are given. We further provide our opinions on normal tissue delineation and organisational and responsibility questions in the process of target volume delineation. This guideline intends to contribute to the standardisation and optimisation of the process of RT treatment planning for clinical practice and prospective studies.

- **Planning ct scan.**
- Scan in treatment position and should incluse IV iodine contrast
- 4D-CT scan is reccomended
- Additional imaging for RT planning
- PET/TC scan is reccomended and should be done preferably in planning position.
- Gross tumour volume (GTV)
- GTV delineation on the planning CT is mandatory
- Pre-set lung window (W=1600 L=-600) Pre-set mediastinum window (W=400 L=20)
- Lymph nodes malignant by biopsy or considered pathological on PET are delineated as GTV
- Lymph nodes that are FDG-PETpositive and EBUS/EUS negative should be included in the GTV as the false negative rates of EBUS/EUS are high
- CTV of the primary tumour should be created from espansion from the GTV by e.g. 5 -8 mm
- CTV of Lymph nodes with two options: option 1 inclusion of the whole pathologically affected lymph node station option 2 geometric expansion of nodal GTV to CTV in analogy to the primary tumour (5-8 mm)
- PORT: involved anatomical mediastinal lymph node regions, the bronchial stump, the ipsilateral hilum and nodal stations 4 e 7

J Clin Oncol. 2017 Jan 1; 35(1): 56–62.
Published online 2016 Oct 3. doi: 10.1200/JCO.2016.69.1378
PMCID: PMC5455690
PMID: 28034064

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

Stephen G. Chun,[✉] Chen Hu, Hak Choy, Ritsuko U. Komaki, Robert D. Timmerman, Steven E. Schild, Jeffrey A. Bogart, Michael C. Dobelbower, Walter Bosch, James M. Galvin, Vivek S. Kavadi, Samir Narayan, Puneeth Iyengar, Clifford G. Robinson, Raymond B. Wynn, Adam Raben, Mark E. Augspurger, Robert M. MacRae, Rebecca Paulus, and Jeffrey D. Bradley

▸ Author information ▸ Copyright and License information Disclaimer

Table 2.

Dosimetric Factors of 3D-CRT Versus IMRT

Table 2. Dosimetric Factors of 3D-CRT Versus IMRT

Dosimetric Factor	3D-CRT		IMRT		
	Median	Q1-Q3	Median	Q1-Q3	*P*
PTV volume, mL	426.7	298.1-586.5	486.2	347.6-677.3	.005*
Volume of lung excluding CTV, mL	3,331.4	2,676.7-4,045.0	3,215.7	2,754.6-4,020.0	.779*
PTV volume:lung volume ratio	0.13	0.09-0.19	0.15	0.10-0.21	.013*
Minimum dose to PTV, Gy	55.2	49.8-60.2	53.4	48.0-57.3	< .001†
Maximum dose to PTV, Gy	68.8	66.1-80.8	70.2	66.1-80.9	.256†
Dose to cover 95% of PTV, Gy	60.8	60.0-72.3	60.7	60.0-73.0	.088†
PTV covered by 100% Rx dose, %	94.8	87.0-96.4	95.1	92.1-97.0	.058*
Mean lung dose, Gy	18.1	15.4-20.6	17.7	14.4-20.1	.088†
Volume of lung, %					
V5	54.8	43.3-65.9	61.6	52.1-70.4	< .001†
V20	30.5	25.3-35.1	29.9	24.0-34.7	.297†
Mean esophagus dose, Gy	27.6	22.1-32.8	25.6	20.2-32.6	.078†
Volume of esophagus, %					
V20	47.6	39.4-56.9	46.8	36.7-56.7	.466†
V60	19.7	5.2-30.4	18.4	3.6-29.3	.927†
Volume of heart, %					
V20	23.5	7.8-46.0	19.3	5.2-36.5	.049†
V40	11.4	1.7-25.9	6.8	0.6-15.5	.003†
V60	2.4	0.0-8.3	1.4	0.0-5.0	.045†
Volume of heart inside PTV, mL	2.05	0.00-16.46	3.56	0.00-16.73	.183*
Maximum dose outside PTV, Gy	69.9	66.3-80.8	69.55	65.6-79.9	.026†

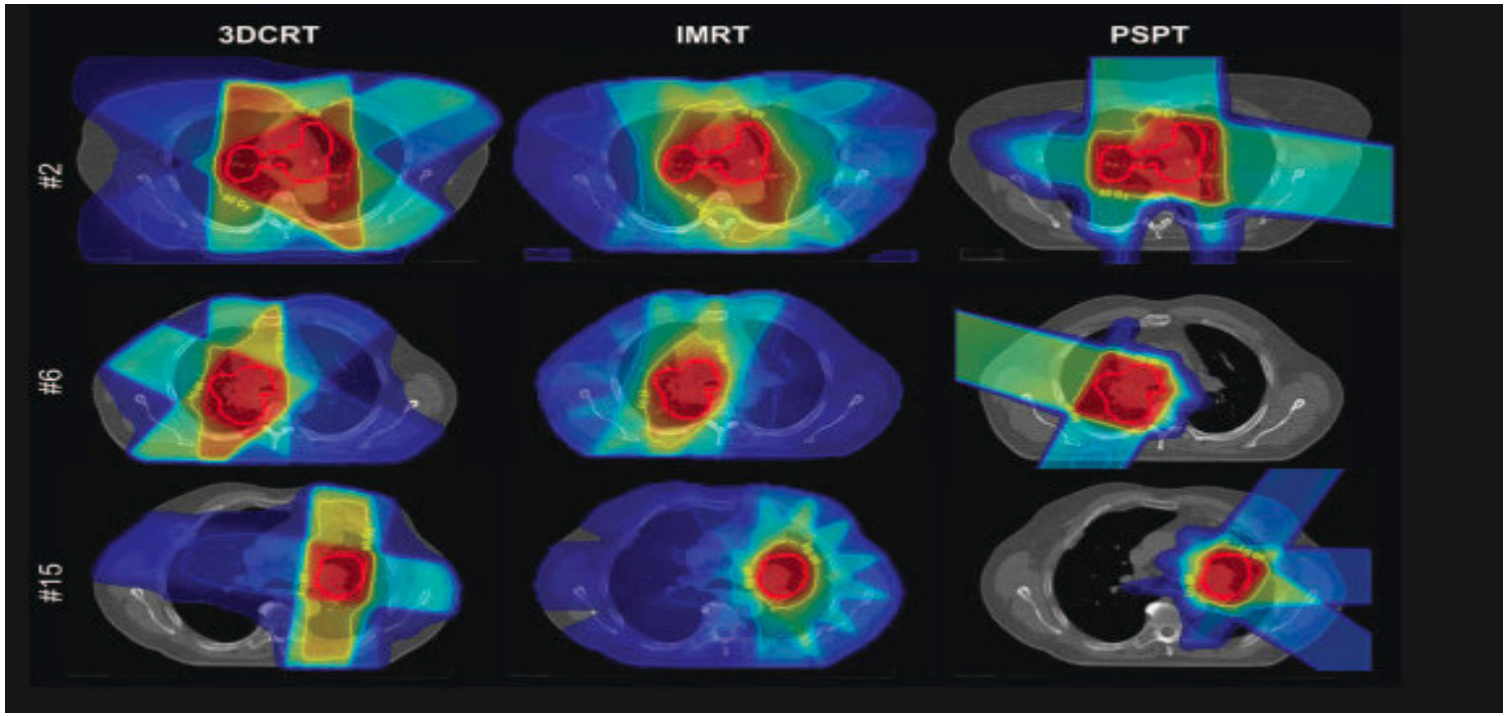
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; CTV, clinical target volume; IMRT, intensity-modulated radiation therapy; PTV, planning treatment volume; Q1, quartile 1; Q3, quartile 3; Rx, prescription; V, volume receiving radiation dose.

**P* value from Wilcoxon test.

†*P* value from Wilcoxon test stratified by radiation therapy dose level (60 *v* 74 Gy).

Conclusion

IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RTOG 0617, which supports routine use of IMRT for locally advanced NSCLC.



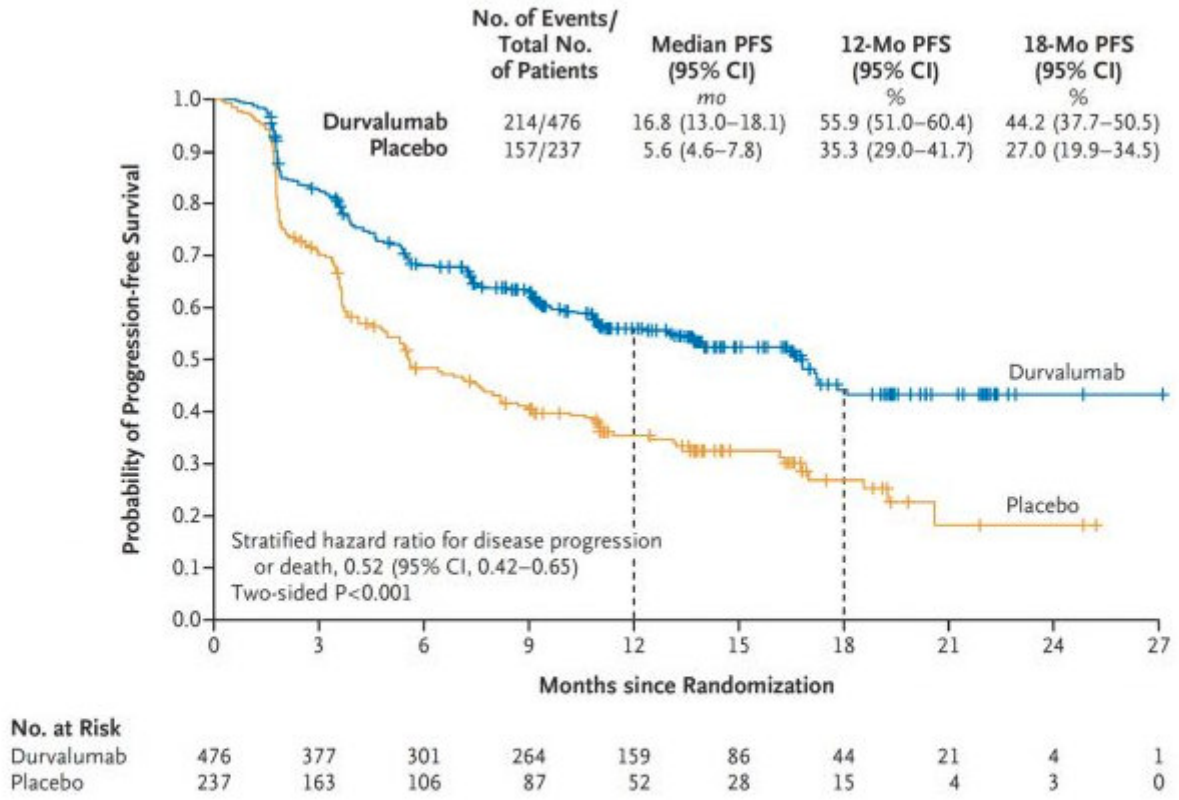
Journal of Thoracic Oncology Volume 7, Issue 1, January 2012, Pages 165-176

DURVALUMAB

The U.S. Food and Drug Administration approved durvalumab on February 16, 2018, for the treatment of patients with stage III NSCLC whose tumors are unresectable and whose cancer has not progressed after treatment with chemoradiation— the first drug for this indication.

The approval was based on the phase III PACIFIC trial, a randomized trial of 713 patients in which sequential treatment with the PD-L1 inhibitor durvalumab was compared to placebo in patients with locally advanced, unresectable stage III NSCLC whose disease had not progressed following platinum-based chemotherapy concurrent with radiation therapy. The median progression-free survival (PFS) for durvalumab was 16.8 months compared to 5.6 months for placebo. Overall survival data have not yet been reported. ✦

PACIFIC DURVALUMAB



Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization. N Engl J Med. 2017 Nov 16;377(20):1919-1929.

Contacts:

Lisa Rivero
Vice President
lrivero@jpa.com| +1 617-657-1305

Becky Bunn, MSc
Public Relations Manager
Becky.Bunn@IASLC.org | +1 720-254-9509

PACIFIC Study Shows Durvalumab Improves Overall Survival in Patients with Unresectable Non-Small Cell Lung Cancer Without Progression after Chemoradiotherapy

Toronto, Canada – September 25, 2018 – Findings from a recent study demonstrate that the PD-L1 inhibitor durvalumab demonstrated statistically significant and clinically meaningful improvement in overall survival (OS) compared with placebo for patients with Stage III, unresectable non-small cell lung cancer (NSCLC) who have not progressed following chemoradiotherapy (CRT). Scott J. Antonia, M.D., Ph.D., department chair of the Thoracic Oncology Department at the H. Lee Moffitt Cancer Center and Research Institute in Tampa and professor of Oncologic Sciences at the University of South Florida College of Medicine, presented these findings today at the IASLC's 19th World Conference on Lung Cancer (WCLC) in Toronto, Canada.

RESULTS Of the 713 patients who underwent randomization, 709 received the assigned intervention (473 patients received durvalumab and 236 received placebo). As of March 22, 2018, the median follow-up was 25.2 months. The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the durvalumab group, as compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided P=0.005). Durvalumab significantly prolonged overall survival, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997; P=0.0025). Updated analyses regarding progression-free survival were similar to those previously reported, with a median duration of 17.2 months in the durvalumab group and 5.6 months in the placebo group (stratified hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.63). The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group (stratified hazard ratio, 0.53; 95% CI, 0.41 to 0.68). A total of 30.5% of the patients in the durvalumab group and 26.1% of those in the placebo group had grade 3 or 4 adverse events of any cause; 15.4% and 9.8% of the patients, respectively, discontinued the trial regimen because of adverse events.

CONCLUSIONS Durvalumab therapy resulted in significantly longer overall survival than placebo. No new safety signals were identified. (Funded by AstraZeneca; PACIFIC ClinicalTrials.gov number, NCT02125461.)

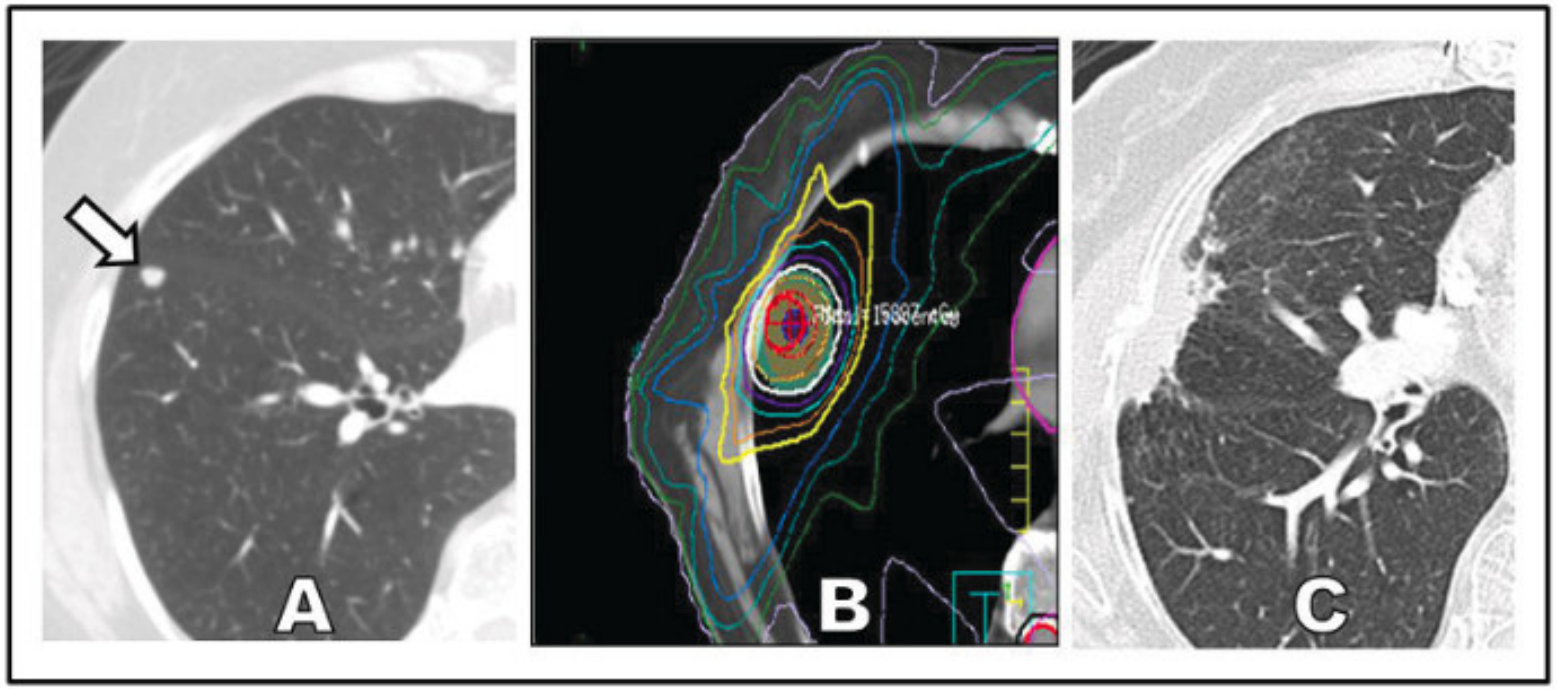
The PACIFIC trial was a randomized, double-blinded, placebo-controlled, multicenter trial of 713 patients in 235 study centers across 26 countries. Of the 709 patients who received treatment, 473 received durvalumab and 236 placebo. As of the data cutoff in March 2018, median follow-up duration was 25.2 months (range, 0.2 - 43.1). After discontinuation, 41 percent and 54 percent in the durvalumab and placebo groups, respectively, received subsequent anticancer therapy; overall, 8.0 percent and 22.4 percent received another immunotherapy.

Results showed that durvalumab significantly improved OS, the second primary endpoint, versus placebo, with the median not reached and 28.7 months, respectively. Durvalumab also improved OS in all pre-specified subgroups and improved secondary endpoints of time to death or distant metastasis (TTDM), time to second progression (PFS2), time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST). These results are significant because PACIFIC is the first trial to show a survival advantage following CRT in this patient population.

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either **a single dose or a small number of fractions.** Specialized treatment planning results in **high target dose and steep dose gradients beyond the target.** The ability to deliver a single or a few fractions of high-dose ionizing radiation with **high targeting accuracy and rapid dose falloff** gradients encompassing tumors within a patient provides the basis for the development of SBRT.

ACR–ASTRO PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY 2009

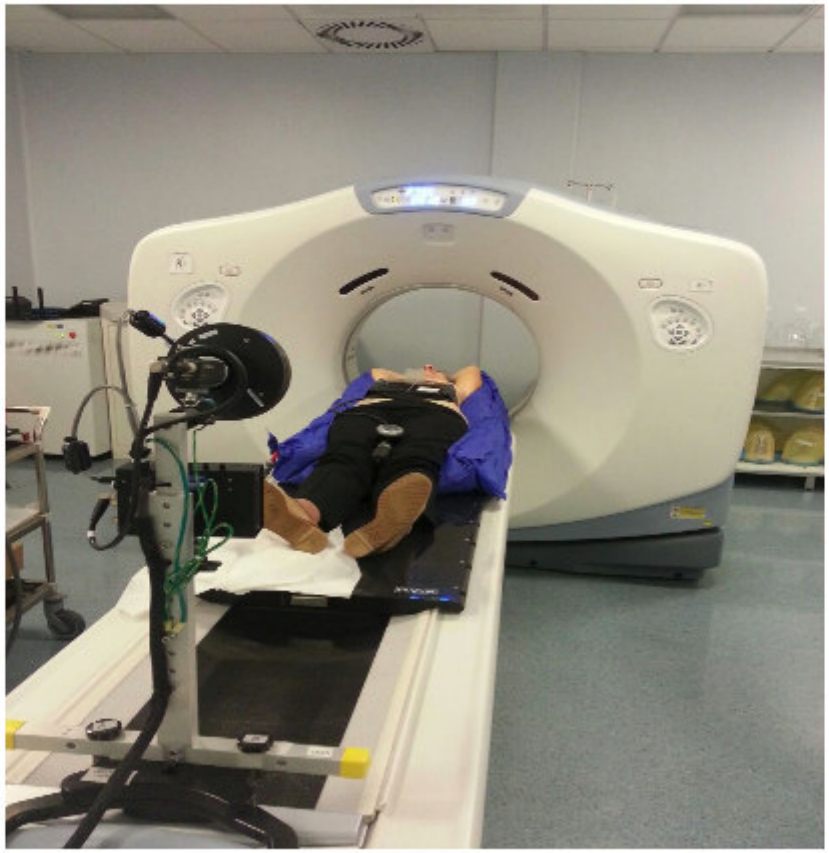
RAPID DOSE FALLOFF



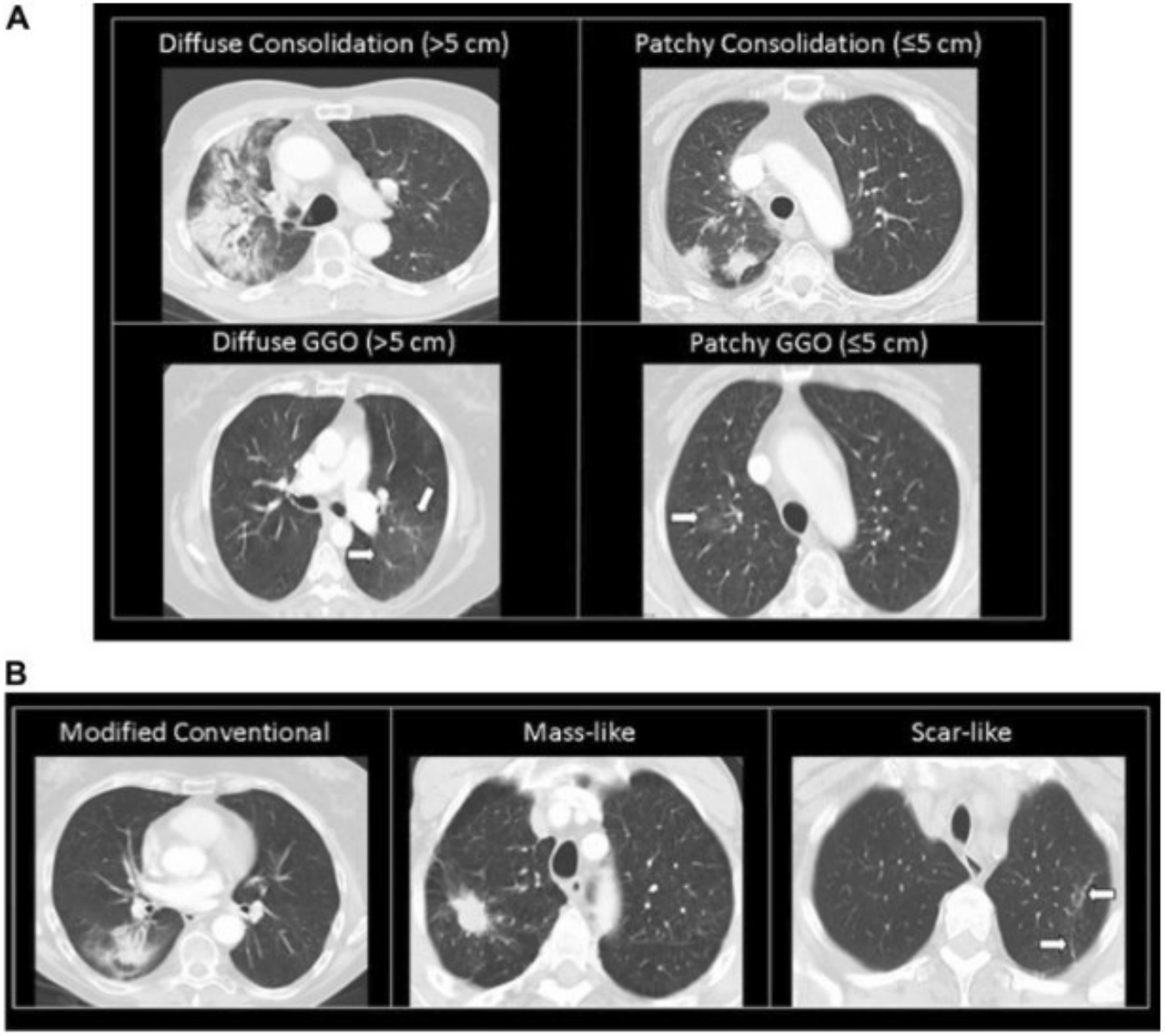
WHOOOOOOOOPS!


MACHINE
OPTIONS

Radioterapia HPG23



- Radiological changes after SBRT
- Radiation fibrosis (later than 6 months)
- (Koenig’s classification, AJR 2002):
- • Modified conventional pattern
- • Mass-like pattern
- • Scar-like pattern
- Modified conventional pattern Mass-like pattern Scar-like pattern


A
Diffuse Consolidation (>5 cm)
Patchy Consolidation (≤5 cm)
Diffuse GGO (>5 cm)
Patchy GGO (≤5 cm)
B
Modified Conventional
Mass-like
Scar-like

- Highly palatable for patients • Highly flexible (different anatomic sites) • Outpatient • 20-60 minutes per treatment • Entire course Rx in 1-2 weeks • 1-8 treatments qd • No sedation or anesthesia (painless) • Immediate return to activities

TABLE III. Summary of suggested dose constraints for various critical organs. Note that for serial tissues, the volume-dose constraints are given in terms of the critical maximum tissue volume that should receive a dose equal or greater than the indicated threshold dose for the given number of fractions used. For parallel tissue, the volume-dose constraints are based on a critical minimum volume of tissue that should receive a dose equal to or less than the indicated threshold dose for the given number of fractions used.

		One fraction		Three fractions		Five fractions		
Serial tissue	Max critical volume above threshold	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	End point (≥Grade3)
Optic pathway	<0.2 cc	8	10	15.3 (5.1 Gy/fx)	17.4 (5.8 Gy/fx)	23 (4.6 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			9		17.1 (5.7 Gy/fx)		25 (5 Gy/fx)	Hearing loss
Brainstem (not medulla)	<0.5 cc	10	15	18 (6 Gy/fx)	23.1 (7.7 Gy/fx)	23 (4.6 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord and medulla	<0.35 cc	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<1.2 cc	7		12.3 (4.1 Gy/fx)		14.5 (2.9 Gy/fx)		
Spinal cord subvolume (5–6 mm above and below level treated per Ryu)	<10% of subvolume	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
Cauda equina	<5 cc	14	16	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuritis
Sacral plexus	<5 cc	14.4	16	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus[b]	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Brachial plexus	<3 cc	14	17.5	20.4 (6.8 Gy/fx)	24 (8 Gy/fx)	27 (5.4 Gy/fx)	30.5 (6.1 Gy/fx)	Neuropathy
Heart/pericardium	<15 cc	16	22	24 (8 Gy/fx)	30 (10 Gy/fx)	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10 cc	31	37	39 (13 Gy/fx)	45 (15 Gy/fx)	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and large bronchus[b]	<4 cc	10.5	20.2	15 (5 Gy/fx)	30 (10 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stenosis/fistula
Bronchus-smaller airways	<0.5 cc	12.4	13.3	18.9 (6.3 Gy/fx)	23.1 (7.7 Gy/fx)	21 (4.2 Gy/fx)	33 (6.6 Gy/fx)	Stenosis with atelectasis
Rib	<1 cc	22	30	28.8 (9.6 Gy/fx)	36.9 (12.3 Gy/fx)	35 (7 Gy/fx)	43 (8.6 Gy/fx)	Pain or fracture
	<30 cc			30.0 (10.0 Gy/fx)				
Skin	<10 cc	23	26	30 (10 Gy/fx)	33 (11 Gy/fx)	36.5 (7.3 Gy/fx)	39.5 (7.9 Gy/fx)	Ulceration
Stomach	<10 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum[b]	<5 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
	<10 cc	9		11.4 (3.8 Gy/fx)		12.5 (2.5 Gy/fx)		
Jejunum/ileum[b]	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Enteritis/ obstruction
Colon[b]	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/fistula
Rectum[b]	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/fistula
Bladder wall	<15 cc	11.4	18.4	16.8 (5.6 Gy/fx)	28.2 (9.4 Gy/fx)	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	Cystitis/fistula
Penile bulb	<3 cc	14	34	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10 cc	14		21.9 (7.3 Gy/fx)		30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6	18.6 (6.2 Gy/fx)			23 (4.6 Gy/fx)		Malignant hypertension

OLIGOMETASTATIC STATE

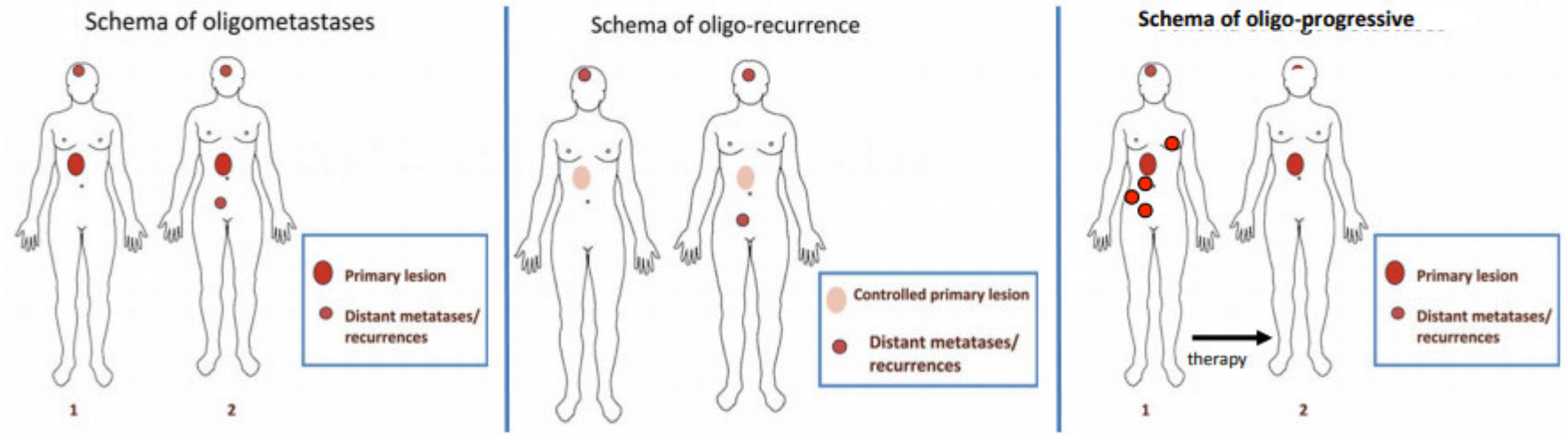
- • Oligometastatic state: limited number of metastases in a limited number of organs, all amenable to radical local therapy

- An attractive consequence of the oligometastatic state is that some patients should be amenable to a "potentially curative therapeutic strategy”

Weichselbaum & Hellmann. J Clin Oncol 1995;13:8
Weichselbaum & Hellmann. Nat Rev Clin Oncol 2011;8:378

Distinct cohorts of oligometastatic disease

"oligometastases" = diagnosed with oligometastatic disease
"oligorecurrence" = relapsed oligometastatic disease
"oligoprogressive" = oligometastatic disease after cytoreductive therapy



→ These cohorts have probably different prognoses

Weichselbaum & Hellmann. Nat Rev Clin Oncol 2011;8:378

Tumori. 2018 Jun;104(3):148-156. doi: 10.1177/0300891618766820. Epub 2018 Apr 11.

Stereotactic body radiotherapy for lung oligometastases: Literature review according to PICO criteria.

Alongi F[1,2], Mazzola R[1], Figlia V[1], Guckenberger M[3].

Author information

Abstract

Exhaustive criteria and definitive data to identify the ideal lung oligometastatic patient as a candidate for stereotactic body radiotherapy (SBRT) are lacking. Three distinct cohorts of oligometastatic patients could be distinguished: (1) patients with upfront diagnosis of oligometastases (synchronous or metachronous); (2) patients with oligorecurrent disease in terms of relapsed oligometastatic phase; (3) oligoprogressive patients after cytoreductive treatment. The aim of the present review is to analyze available data concerning the efficacy/safety of SBRT for oligometastatic/oligoprogressive/oligorecurrent lung metastases.

KEYWORDS: PICO criteria; SBRT; lung oligometastases; review

67 pubblications
869 patients
1142 treated lung metastases
4 studies prospective, remaining retrospective
569 oligometastases
175 oligorecurrent
81 oligoprogressive
Most of selected studies included patients affected by 1-3 lung lesion

BED greater than or equal to 100 Gy
Time from primary treatment to SBRT from 12 to 48 months

Radiother Oncol. 2013 Jun;107(3):409-13. doi: 10.1016/j.radonc.2013.05.024. Epub 2013 Jun 14.

Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy?

Widder J[1], Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJ, Langendijk JA.

Author information

Abstract

BACKGROUND AND PURPOSE: Stereotactic ablative radiotherapy (SABR; or stereotactic body radiotherapy, SBRT) emerges as treatment option for pulmonary oligometastatic disease (OMD), but there are no studies comparing SABR with pulmonary metastasectomy (PME). We analysed consecutive patients referred via a university-hospital based multidisciplinary team.

MATERIAL AND METHODS: Patients were offered PME as first choice and SABR in case they were considered to be less suitable surgical candidates. Overall survival was the primary endpoint. Secondary endpoints were progression-free-survival, local control of treated metastases, and freedom-from-failure of a local-only treatment strategy without systemic therapy.

RESULTS: From 2007 until 2010, 110 patients were treated and analysed (PME, n=68; SABR, n=42). Median follow-up time was 43 months (minimally, 25). Estimated overall survival rates at one, three, and five years were 87%, 62%, and 41% for PME, and 98%, 60%, and 49% for SABR, respectively (logrank-test, p=0.43). Local control at two years was 94% for SABR and 90% for PME. Progression-free survival was 17% at three years, but 43% of the patients still had not failed a local-only treatment strategy.

CONCLUSIONS: Although SABR was second choice after PME, survival after PME was not better than after SABR. Prospective comparative studies are clearly required to define the role of both, SABR and PME in OMD.

Comparison 110 patients PME first choice, SABR if considered less suitable surgical
OS one, three, five years 87%,62%,41% for PME and 98%,60%,49% for SABR
LC at two years 94% SABR 90% PME

Jpn J Clin Oncol. 2016 Jul;46(7):687-91. doi: 10.1093/jjco/hyw047. Epub 2016 May 9.

Lung stereotactic radiotherapy for oligometastases: comparison of oligo-recurrence and sync-oligometastases.

Yamashita H[1], Niibe Y[2], Yamamoto T[3], Katsui K[4], Jingu K[3], Kanazawa S[4], Terahara A[5], Nakagawa K[1].

Author information

Abstract

BACKGROUND: Oligometastases can be divided into sync-oligometastases and oligo-recurrence. The difference is whether the primary site is uncontrolled or controlled. The goal of this multicenter study was to evaluate treatment outcomes and factors affecting survival after stereotactic body radiotherapy for pulmonary oligometastases.

METHODS: The information after stereotactic body radiotherapy from January 2004 to April 2014 was retrospectively collected. Ninety-six patients (65 males, 31 females) were enrolled. Ten cases (10%) were sync-oligometastases, 79 cases (82%) were oligo-recurrences and 7 (7%) were unclassified oligometastases with <6 months of disease-free interval. The median disease-free interval between initial therapy and stereotactic body radiotherapy was 24 months. The median calculated biological effective dose was 105.6 Gy.

RESULTS: The median follow-up period was 32 months for survivors. The 3-year overall survival and relapse-free survival rates were 53% and 32%, respectively. No Grade 5 toxicity occurred. The median overall survival was 23.9 months for sync-oligometastases and 66.6 months for oligo-recurrence (P = 0.0029). On multivariate analysis, sync-oligometastases and multiple oligometastatic tumors were significant unfavorable factors for both overall survival and relapse-free survival.

CONCLUSIONS: In stereotactic body radiotherapy for oligometastatic lung tumors, the state of oligo-recurrence has the potential of a significant prognostic factor for survival.

96 patients
Between initial therapy and SABR median 24 months
OS 23.9 months for sync-oligometastases and 66.6 months for oligorecurrence
State of oligo-recurrence has the potential of significant factor for OS and relapse-free survival

Outcomes and treatment -related toxicities of the analyzed studies.

1,2,3 year LC after SBRT varied from 62% to 97%, 79% to 94% and 74% to 90%
1,2,3 year OS after SBRT varied from 76% to 98%, 31% to 76% and 53% to 73%

Tolerability following SBRT >= grade 3 toxicity was registred within 3% of cases as symptomatic pneumonitis

Yamashita better oligorecurrent metastases vs sync-oligometastases

Recent study of Helou :

Confirm the role of SBRT in the specific setting of lung oligoprogressive metastases. (IJROBP 2017;98:419-427)

Conclusions:

- Different cohorts of oligometastatic patients (synchronous or metachronous,oligoreccurent or oligoprogressive) probably have different prognoses.

-Oligometastatic lung lesions are potentially treated with different local treatments, including SBRT,surgery, or radiofrequency.

-No differences in LC and OS between surgery and SBRT

-Several prognostic factors: colorectal histology,larger tumours, BED inferior of 100 were associated with a higher rate of local failure.

In summary , SBRT allow a major benefit for lung oligometastatic patients with noncolorectal histology, DFI > 24 months, when controlling the primary tumour site, small lesions, and limited number of lesions.

TLCR Translational Lung Cancer Research
An open access journal focusing on closing the gap between "bench and bedside"

Indexed by SCIE

Article Abstract

Combining stereotactic body radiation therapy with immunotherapy: current data and future directions

Authors: Alexander J. Lin, Michael Roach, Jeffrey Bradley, Clifford Robinson

Abstract

Stereotactic body radiation therapy (SBRT) offers excellent local control of early-stage non-small cell lung cancer (NSCLC), but there currently is a need for tolerable systemic therapy to address regional and distant disease progression. One potential option is immunotherapy, which in metastatic NSCLC has shown promise for sustained disease control in a subset of patients. There is also growing evidence for a clinical synergy between radiation and immunotherapy, with several ongoing trials studying the abscopal effect. This review summarizes the current data in the fast-changing field of immuno-radiation therapy, highlighting updates from recent clinical trials.

Immunotherapy the fourth pillar of oncology
FDA approves antibody target CTLA-4,PD-1, PDL-1
Activation of CTLA-4 and PD-1 receptors on T cells downregulateds the adaptive immune response

Rationale for combinig SBRT with immunotherapy.
SBRT tumour debulking may improve immunotherapy response.

Radiation upregulate cell surface markers
MHC class I (presents intracellular antigens to the cell surface for T cells)
Calreticulin
HMGB1
FAS (immunità innata)
Radiation unfortunately is a double edge sword : deplete circulating lymphocytes.
Abscopal effect immune-mediated: radiate a tumour and create anti tumour effects outside the irradiated field.

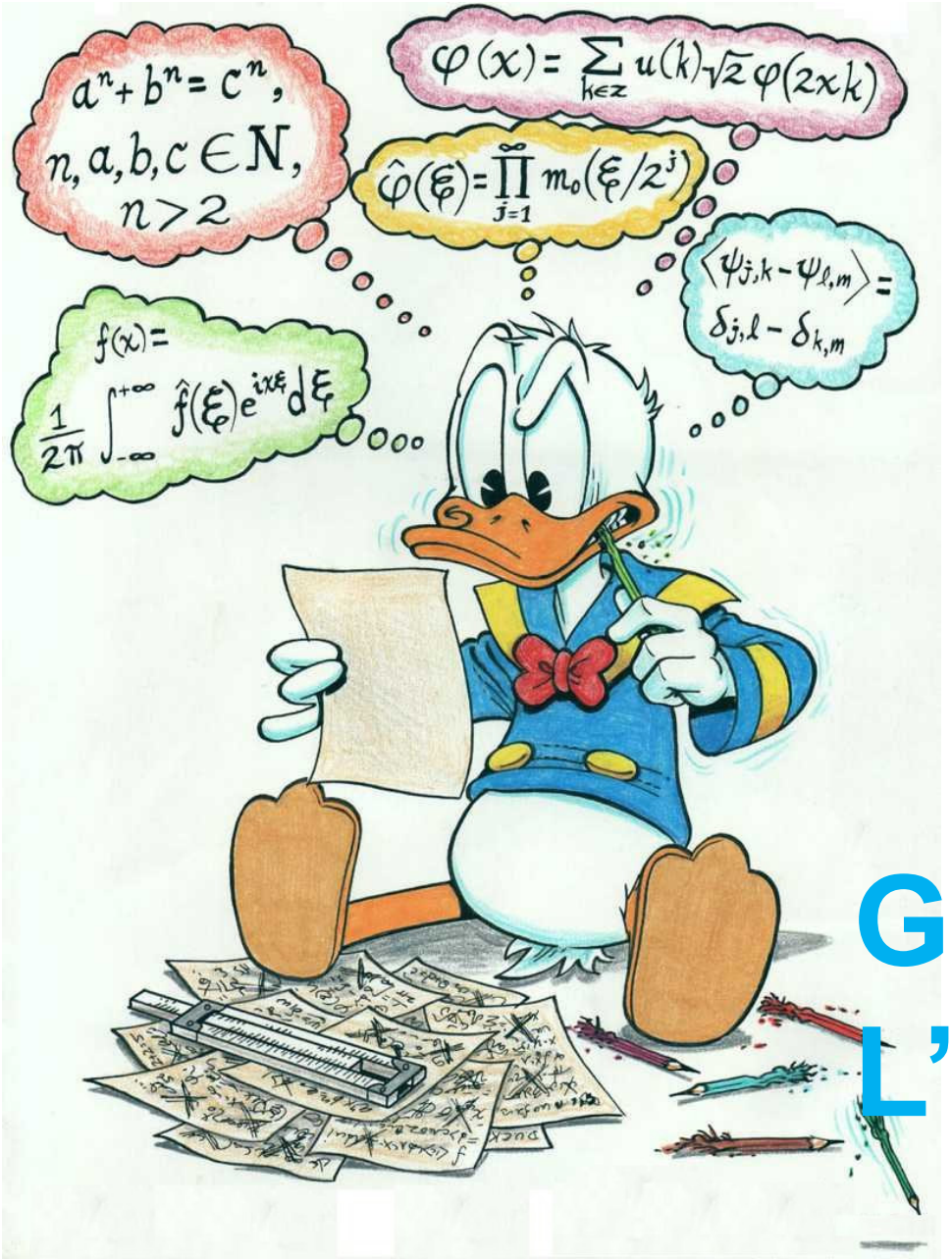
Table 1 Active clinical trials involving SBRT and immunotherapy in metastatic lung cancer

NCT number	Title (study drug if not in title)	Recruitment	Study endpoint	Phase	Enrollment
NCT02239900	Ipilimumab and Stereotactic Body Radiation Therapy (SBRT) in Advanced Solid Tumors	MD Anderson, Houston, TX; recruiting 120	Safety, irRC response rate	1–2	Active, closed to enrollment
NCT02444741	Pembrolizumab and Stereotactic Body Radiation Therapy (SBRT) in Patients With Non-Small Cell Lung Cancer (NSCLC)	MD Anderson, Houston, TX; recruiting 104	Safety, irRC response rate, PFS	1–2	Open
NCT02839265	FLT3 Ligand Immunotherapy and Stereotactic Radiotherapy for Advanced Non-small Cell Lung Cancer (FLT3)	Albert Einstein, NYC, NY; recruiting 29	4-month PFS	2	Open
NCT03168464	Radiation and Immune Checkpoints Blockade in Metastatic NSCLC (nivolumab/ipilimumab)	Cornell, NYC, NY; recruiting 45	Response rate, PFS, OS	1–2	
NCT03275597	Phase Ib Study of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Non-small Lung Cancer (NSCLC) With Dual Immune Checkpoint Inhibition (durvalumab/tremelimumab)	University of Wisconsin, Madison; recruiting 21	Safety, PFS, OS	1	Open
NCT03223155	Evaluate Concurrent Or Sequential Ipilimumab, Nivolumab, and Stereotactic Body Radiotherapy in Patients With Stage IV Non-Small Cell Lung Cancer	University of Chicago, IL; recruiting 80	Safety, response rate	1	Open
NCT03313804	Priming Immunotherapy in Advanced Disease With Radiation (any checkpoint inhibitor)	University of Kentucky, Lexington; recruiting 57	6-month PFS	2	Open
NCT03035890	Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer (nivolumab, pembrolizumab, or atezolizumab)	West Virginia University; recruiting 33	Response rate, OS, PFS, QoL	1	
NCT02831933	Trial of Stereotactic Body Radiation and Gene Therapy Before Nivolumab for Metastatic Non-Small Cell Lung Carcinoma (ENSIGN)	Methodist Hospital, Houston, TX; recruiting 29	Response rate, PFS, OS	2	Open
NCT03224871	A Pilot Study of Interlesional IL-2 and RT in Patients With NSCLC (nivolumab/pembrolizumab)	University of California, Davis; recruiting 30	Safety, DFS	1	Open
NCT03158883	Avelumab and Stereotactic Ablative Radiotherapy in Non-responding and Progressing NSCLC Patients	University of California, Davis; recruiting 26	Response rate, PFS, OS, irRC	1	Open
NCT03176173	Radical-Dose Image Guided Radiation Therapy in Treating Patients With Metastatic Non-small Cell Lung Cancer Undergoing Immunotherapy (nivolumab, pembrolizumab, or atezolizumab)	Stanford University, CA; recruiting 85	PFS, OS, ctDNA changes	2	Open

Conclusions:

In the marriage of SBRT with immunotherapy, we are still in the honeymoon period.

Time will tell if these early promise will last.



GRAZIE PER L'ATTENZIONE