#ESMOUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

ESMO HIGHLIGHTS

27 SEPTIEMBRE - 1 OCTUBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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BARCELONA

Novedades en cáncer de pulmón no microcítico localizado y localmente avanzado (I)

Dr. Fabio Franco

Con la colaboración de:
Bristol-Myers Squibb
illumina
Lilly

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ESMO-ESTRO Collaborative session: RTCT in stage III NSCLC, prevention and management of toxicity including the use of immunotherapy.

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Nutrition before and during CCRT, including treatment and prevention of anorexia.

Prevention and management of “in-field” toxicities: Oesophagus, nausea and vomiting, lung, skin, heart.

Prevention and treatment of fatigue.

Radiotherapy techniques and chemotherapy adjustments to prevent toxicity in the era of immune therapy.

- El abordaje terapéutico del paciente con cáncer de pulmón localmente avanzado requiere de un esfuerzo dirigido a determinar los potenciales grupos de paciente con mayor riesgo de toxicidad.

- El significativo aumento de la supervivencia en este grupo de pacientes con terapia combinada de RT/QT seguida de IO, probablemente se asociará a un potencial aumento de los eventos adversos tardíos.

- Factores clínicos a tener en cuenta:
  - Edad.
  - Comorbilidades, principalmente los FRCV y neumopatías.
  - Factores asociados al tumor (tamaño, localización e histología).

- Factores determinantes del tratamiento tanto sistémico como de RT, así como las técnicas.

Erasmus MC Cancer Institute

NSCLC) treated in daily clinical practice: **it is time for cardiovascular screening and follow-up!**

30% of patients with stage III NSCLC have pre-existing cardiac comorbidity.

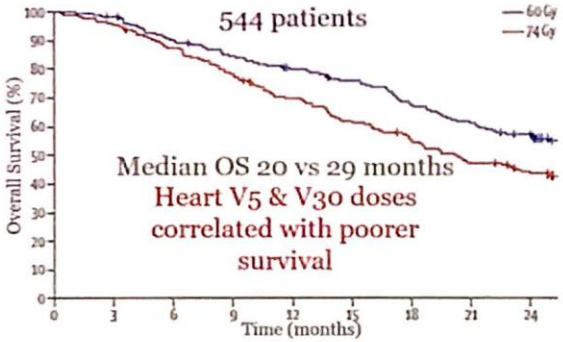
33% develops a new cardiac event during treatment or within 5 years of follow up.

Pre-existent cardiac comorbidity and WHO PS ≥ 2 are significant predictors for cardiac events

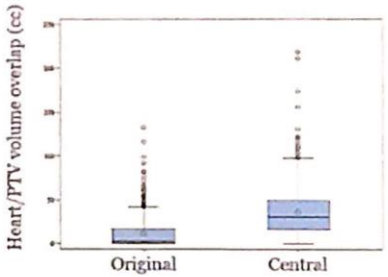
NOTE: 30% of patients with no clinical risk factors develop a cardiac event, further studies are indicated to identify predicting factors for cardiac events in these patients.

Radiation Induced Cardiac Toxicity

RTOG 0617: Stage III NSCLC 60 Gy vs 74 Gy +/- Cetuximab



Cardiac contours inconsistent



Bradley et al Lancet Oncol 2015;

Gore et al ASTRO 2016;

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESTRO

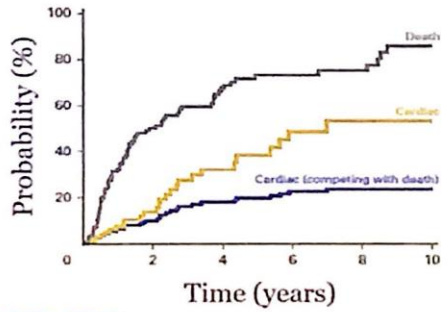
Cardiac Dose is Related to Cardiac Events

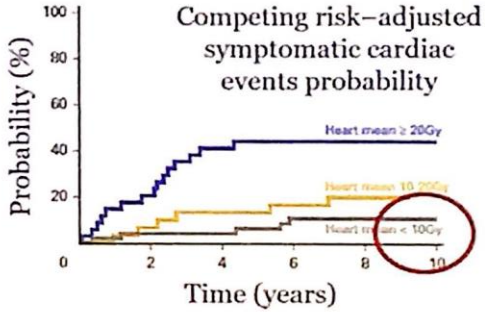
112 good PS patients from 6 CRT prospective trials
Symptomatic cardiac events 23% at median of 26 months

Higher baseline cardiac risk
- Presence of coronary artery disease
- Higher WHO/ISH 10-year risk of cardiovascular event score

Higher heart doses

Both baseline cardiac risk and heart dose were independent risk factors on multivariate analysis





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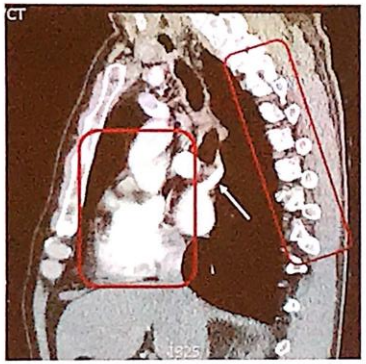
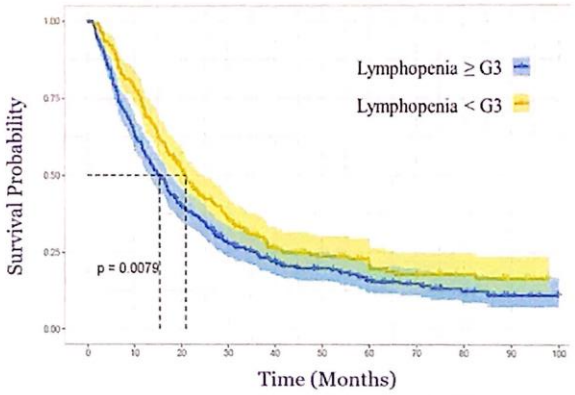
Wang et al JCO 2017;

ESTRO

Radiotherapy-related lymphopenia affects OS in patients with lung cancer. Abravan A et al, ESTRO 2019.

Dose to Lymphocyte Pool?





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Abravan et al ESTRO 2019;

ESTRO

386 pacientes con CP tratados con intención curativa RT.

Todos tenían linfocitos basales normales y se definieron 2 grupos, con y sin linfopenia ≥ G3.

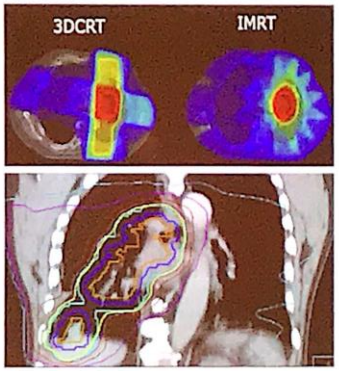
Se analizaron datos clínicos, el volumen de tratamiento, los linfocitos basales, la dosis prescrita y la histología.

La linfopenia ≥ G3 durante la RT es un factor de riesgo significativo en supervivencia en pacientes con CP y requiere un manejo cuidadoso.

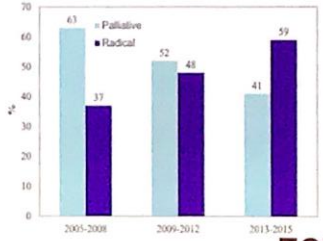
Minimizando el V20 en vértebras y la dosis cardíaca media.

Control estricto de linfocitos y uso de antibióticos profilácticos.

How Can Advances in RT Planning Help?



Impact of IMRT on curative-intent RT:
'Big data' analysis of 8855 patients
2005-8: Pre IMRT partial access to IMRT (n=2872)
2009-12: - limited access to IMRT (n= 3344)
2013-2014: ~Full access to IMRT 2639



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Chan et al BTOG 2017;

ESTRO

How Can Advances in RT Delivery Help?

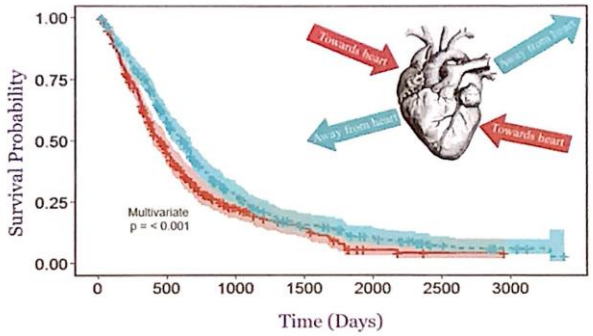
780 NSCLC & 177 Oesophageal patients

3D CBCTs on D1-3 then weekly

5mm action threshold online

Mean residual setup error over the whole course of treatment

Direction of shift relative to heart: away or towards



Increased risk of death with increasing residual shifts towards the heart

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Johnson-Hart et al IJROBP2018;

ESTRO

Inclusión de estudios nuevas áreas de estudio que nos ayuden a determinar grupos de riesgo y factores predictivos de respuesta y toxicidad (BigData).

Asegurar una adecuada recogida de datos sobre las técnicas, volúmenes y dosis de RT en los estudios de terapia combinada.

Desarrollar estudios que ayuden a conocer mejor la fisiopatología de los daños generados por la RT en los tejidos sanos, incluidas subestructuras y ampliar la búsqueda de biomarcadores predictivos.

Rol of Imagin Follow-up: IFCT-0302.

ESMO Guidelines

IFCT 0302

- Patients should be offered smoking cessation
- Patients should be followed for treatment-related complications, detection of treatable relapse or occurrence of SPLC
- q6 months for 2 yrs: history, physical examination and —preferably contrast enhanced— spiral chest CT at 12 and 24 months. Thereafter an annual visit including history, physical examination and chest CT to detect SPC **[III prospective cohort studies, B moderate evidence, limited clinical benefit]**
- Follow-up PET-CT is not recommended [II, D]

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Postmus P, Ann Oncol 2017

Study Design

IFCT 0302 IFCT

Months	Min	Max
6	CXR	Chest CT
12	CXR	Chest CT
18	CXR	Chest CT
24	CXR	Chest CT
30		
36	CXR	Chest CT
42		
48	CXR	Chest CT
54		
60	CXR	Chest CT

Minimal follow-up (Min):

- History + physical examination
- Chest X ray (CXR)
- Only if symptoms or abnormal CXR: CT scan allowed

Maximal follow-up (Max):

- History + physical examination
- Chest X ray
- **CT scan + contrast** (Thorax + upper abdomen)
- Fiberoptic bronchoscopy (mandatory for squamous + large cell carcinomas)

Stratification:
- center
- stage
- histology
- perioperative treatments

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ClinicalTrials.gov number: NCT00198341

Criterios de inclusión:
Pacientes operados de NSCLC, estadio I-IIIA, T4N0-2 (TNM 6ª ed)

No otros antecedentes oncológicos.

Objetivo primario: OS.

Objetivos secundarios: DPS, supervivencia hasta recaída o 2º primario, QoL y coste-efectividad.

Final Analysis

IFCT 0302

- 1775 pts included between Jan 2005 and Nov 2012
- 1st interim analysis: 31 Dec. 2013 with 388 events (39%)
- 2nd interim analysis: 31 Dec. 2015 with 637 events (65%)
- **Final analysis:**
  - End point date: 30 Nov 2016
  - 747 events (75%)
  - Median follow-up (reverse I

Patient Characteristics

IFCT 0302

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1775 pts (Jan 2005-Nov 2012)	Min N=888 (%)	Max N=887 (%)
Gender: Men	678 (76)	677 (76)
Median age (range)	63 (37-88)	63 (34-87)
Smoking: never smokers	68 (8)	80 (9)
Histology		
Squamous	302 (34)	304 (34)
Adenocarcinoma	504 (57)	503 (57)
Large cell	50 (6)	44 (5)
Clinical stage		
I-II	725 (82)	724 (82)
III	161 (18)	162 (18)

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Ineligibles: 72 pts (4%) (prior/conc cancer 31 pts, incomplete resection 14 pts, time from surgery 11 pts, TNM 11 pts, missing consent 5 pts)

Treatments

	Min	Max
Surgery		
Lobectomy	758 (86)	775 (88)
Pneumonectomy	111 (12)	95 (11)
Segmentectomy	16 (2)	15 (2)
Preop CT and/or RT	110 (12)	116 (13)
Postop CT and/or RT	342 (39)	350 (39)
Preop and/or postop RT	61 (6.9)	60 (6.8)

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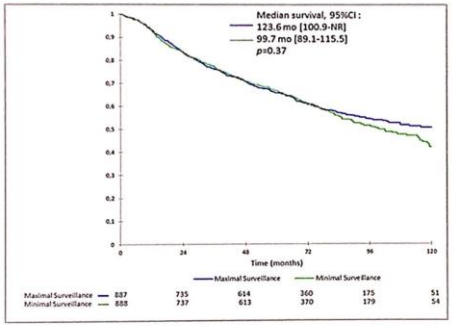
Overall Survival

IFCT 0302



Survival rate (95% CI)	3 years	5 years	8 years
Min	77.3% (74.5 – 80%)	66.7% (63.6 – 69.9%)	51.7% (47.8 – 55.5%)
Max	76.1% (73.3 – 78.9%)	65.8% (62.6 – 68.9%)	54.6 % (50.9 – 58.3%)

- HR_{Max} = 0.94 [0.81-1.08]
- HR_{Max} adjusted = 0.95 [0.82-1.09]

Median follow-up: 7 yrs 2 mths (min: 4 years)

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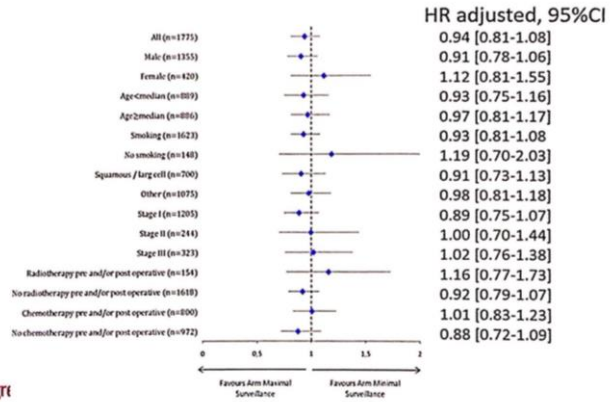
Overall Survival: Subgroup Analyses



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Recurrences

IFCT 0302

	Min	Max	p
recurrences	245 (27.6%)	291 (32.8%)	0.02
Symptomatic	203 (82.9%)	163 (56%)	<0.0001
Ipsilateral lung	103 (50.7%)	96 (58.9%)	NS
Controlateral lung	61 (30.0%)	65 (39.9%)	0.05
Brain	72 (35.5%)	68 (41.7%)	NS
Beyond 2 yr	75 (30.6%)	80 (27.5%)	NS
Surgery only	13 (5.3%)	37 (12.7%)	0.003
Radiotherapy only	26 (10.6%)	37 (12.7%)	NS

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Second Primary Cancers

IFCT 0302

	Min	Max	p
2nd primary cancers	101 (11.4%)	97 (10.9%)	NS
Symptomatic	64 (63.4%)	37 (38.1%)	<0.0001
Sites			
Lung	26 (25.7%)	40 (41.2%)	0.02
Prostate	15 (23.4%)	11 (29.7%)	NS
ENT	12 (18.7%)	7 (18.9%)	NS
Lung, beyond 2 yr	16 (61.5%)	23 (57.5%)	NS
Lung, surgery only	5 (19.2%)	18 (45%)	0.03
Radiotherapy only	3 (11.5%)	1 (2.5%)	NS

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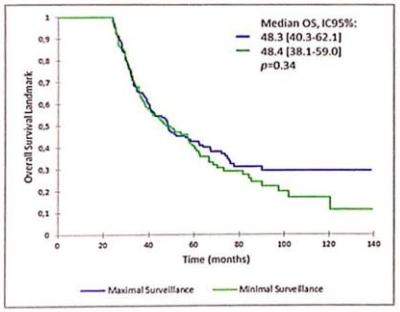
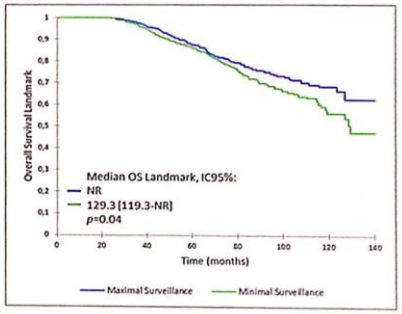
Exploratory Analysis

IFCT 0302

- Pts with a recurrence at 24 mos



- Pts with NO recurrence at 24 mos



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Interaction recurrence-follow-up arm: p<0.0001

Conclusiones IFCT-0302 trial:

Primer estudio randomizado que evalúa el papel del TC de tórax en el seguimiento de pacientes con NSCLC resecado.

Existe una tendencia a un diagnóstico más temprano de las recurrencias y los 2º tumores primarios pero sin impacto significativo en OS.

Existe un potencial beneficio en el seguimiento a largo plazo con TC dado que permite realizar más cirugías en recurrencias y 2º primarios.