Incidental VTE. Who should we anticoagulate?

Anthony Maraveyas

VTE General Background

- VTE incidence is about 1:1000 persons annually
- >250,000 admissions for VTE annually
- >100,000 people die of PE annually
- >90% of PE's arise from lower limb DVT
- 50% of DVT at diagnosis harbors PE
  - **Only 33-40% of these are symptomatic**
- **About 70% of symptomatic PE will have a LL DVT at investigation**

Cronin C.G. et al Am J. Roentgenol. 2007 189: 162-17

Natural acute history of untreated Pulmonary Embolism

- 10% of symptomatic PE are fatal within 1 hour of first symptoms.
  - Clinical diagnosis of PE is established in a minority of patients dying from PE
- Without treatment, 25% of patients die and 50% experience recurrent thrombosis within 3 months[1]

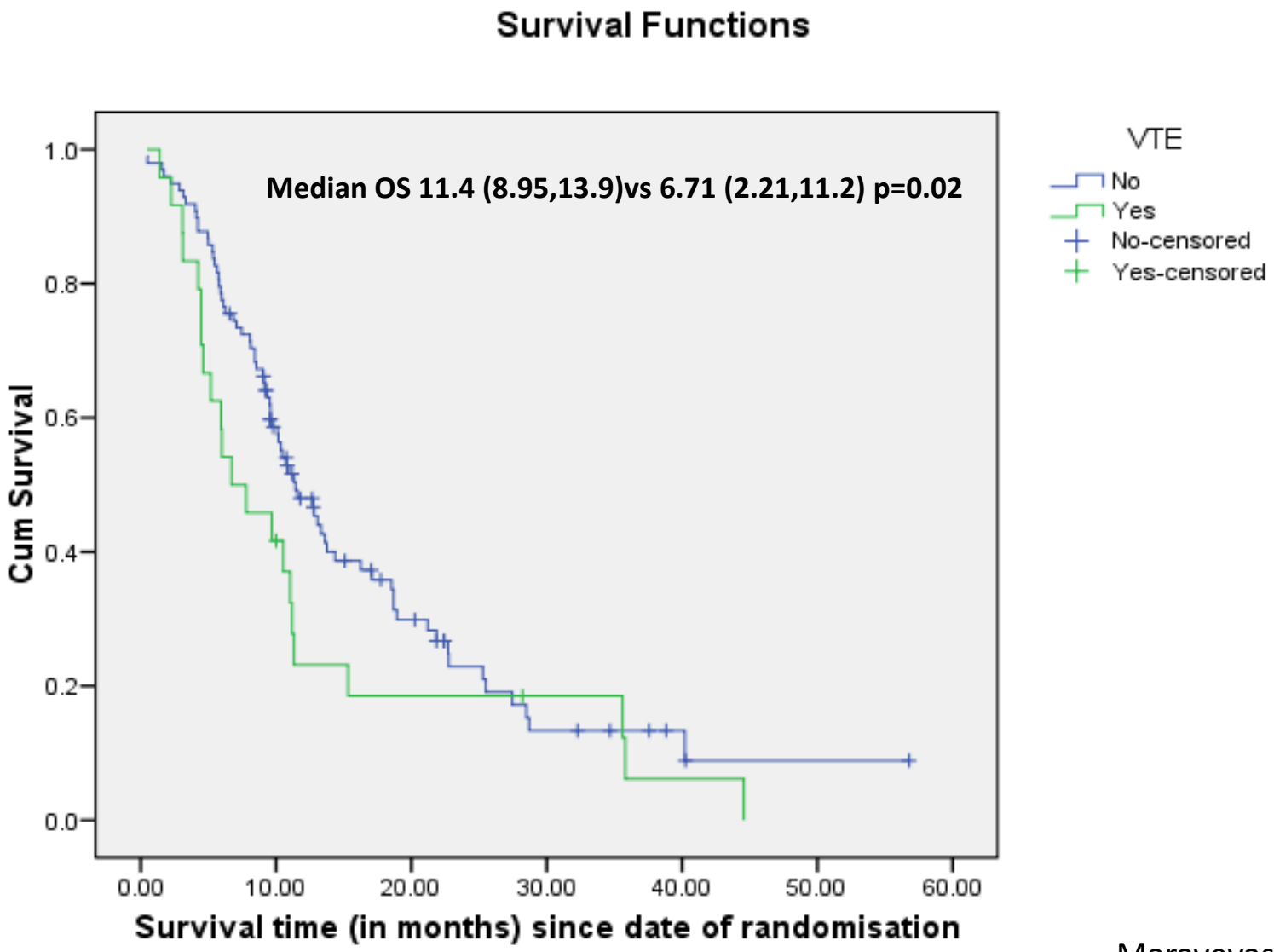
[1]Barritt & Jordan Lancet 1960; 1309-12

CAT: marker of shorter survival

Exposure	Patient Years	Deaths	MR per 100 PY (95%CI)	HR (95% CI)
None	2777713	1750	0.63 (0.60-0.66)	1.0 (Reference)
VTE Only	1317	67	5.1 (4.0-6.4)	2.6 (2.0-3.3)
Cancer Only	**5650**	**721**	**12.7 (11.9-13.7)**	**7.4 (6.8-8.2)**
Cancer & VTE	**131**	**72**	**55.0 (43.6-69.3)**	**31.2 (24.6-39.6)**

Blix K, et al. Eur J Epidemiol. 2014; 29 277-84

CAT: marker of shorter cancer survival



Maraveyas et al EJC 2012

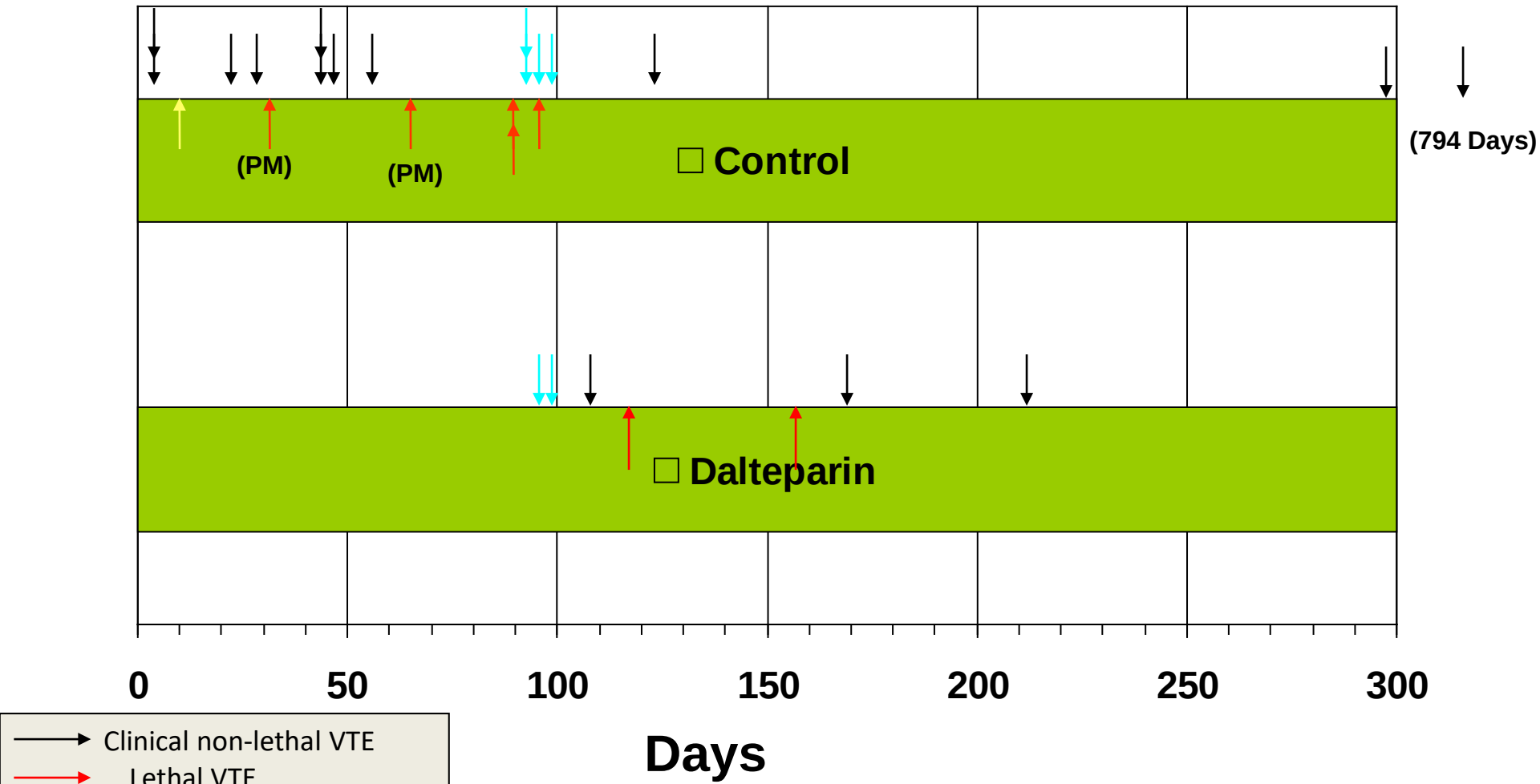
Definition of Incidental PE

- Incidental or Unsuspected interchangeable
  - NOT silent or asymptomatic
- No clinical suspicion of PE
- Diagnosed on imaging done for other reasons
  - Imaging performed with non-angiography protocols
- Has become a particular problem in Cancer patients due to frequent and repetitive scanning

i-PE in Cancer: a clinical problem

- Whole body rather than regional imaging becomes standard of care staging for cancer patients -driven by trial requirements (late 90s early 2000s)-
- Emerges as a problem when the new multi-slice scanners become standard of care (2003-2004)
  - 1mm CT slice thickness

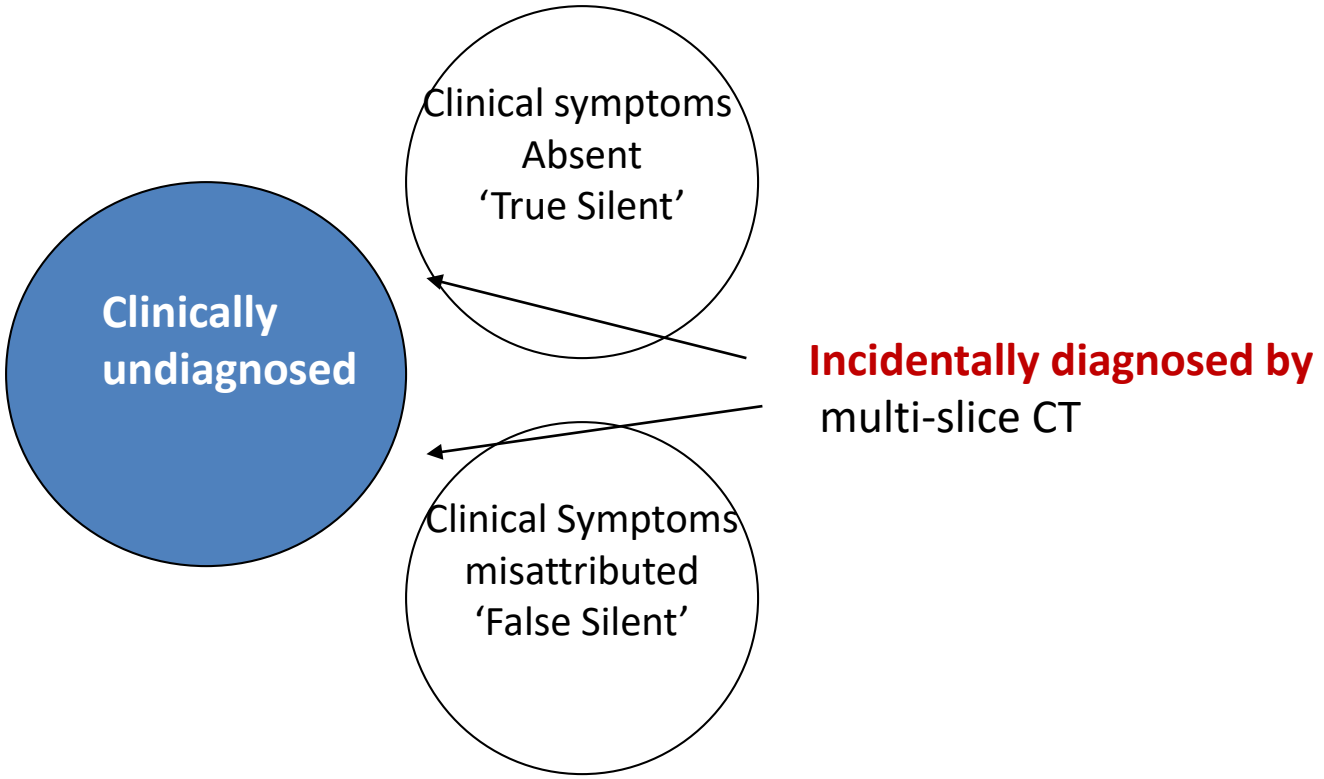
VTE-Time from Randomization



PM= Post-mortem

Maraveyas et al ESMO 2011

What is 'Incidental' PE?



Maraveyas A et al BJC 2009; 100:1837-41

The problem of 'recognition'

- Recognition Gaps
  - Clinically Evident Vs Radiologically evident
  - Clinically suspected Vs Clinically unsuspected
    - But clinically apparent
    - Clinically 'silent' is easier to determine in a non-cancer setting
- Most data derived from trials with active ascertainment
  - Investigators 'went looking' for VTE
    - Venographic and V/Q scan endpoints

How common is incidental in Cancer related scanning?

- HEYNHST (PRH)
  - PE on 2.6% of all routine helical chest CTs in Cancer Patients
    - Sebastian et al Clin Radiol. 2006 61:81-85
  - Literature 1.5% of all routine scans and 2.6-3.4% of scans associated with malignancy
- 6.3% of patients have unsuspected VTE on imaging
  - 25/397 PE, IVC, CI, IF- DVT or Both PE and DVT
    - Cronin C.G. et al Am J. Roentgenol. 2007 189: 162-170
- In HEY (0.5 million) we see between 52-57 iPE a year.

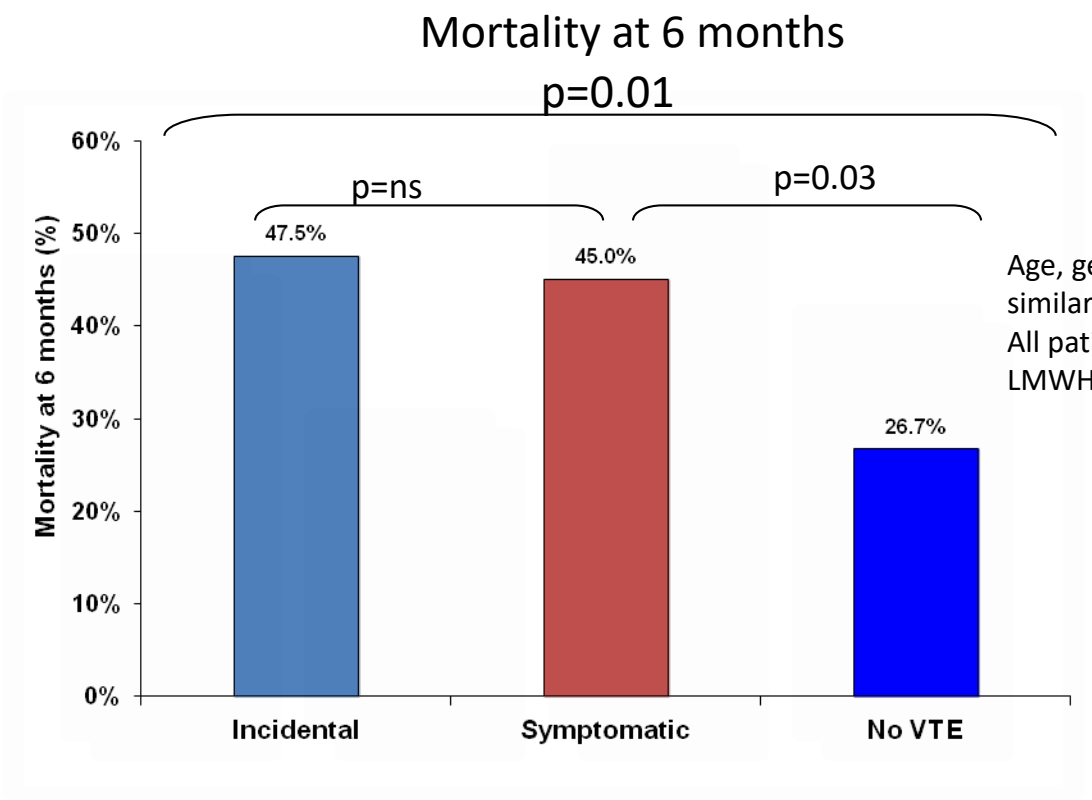
Site of i-PE in CT imaging and symptoms

Site of PE	N	%
Bilateral	59	38
Largest vessel involved		
Main PA or L/R PA	32	21
Lobar PA	53	34
Segmental branches	55	36
Subsegmental branches	**14**	**9**
MD	1	1

Symptoms	N	%
Any new symptoms	66	43
Worsened pre-existing symptoms	29	19
Dyspnoea	74	48
Fatigue	117	76
Chest pain	19	12
Lower limb oedema	51	33
Haemoptysis	6	4
PESI clinical parameters		
Tachycardia	14	9
Hypotension	3	2
Hyperpnoea	0	0
Hypothermia	15	10
Hypoxia	2	1
Altered mental state	2	1

Maraveyas et al. Thrombosis Res 2012 129: S183

Prognostic Relevance of Incidental VTE



Age, gender, cancer site and stage were similar between all 3 groups
All patients with VTE were treated with LMWH or UFH

Conclusions:

- Cancer patients with incidental or symptomatic VTE have a similar mortality rate at 6 months, highlighting the prognostic relevance of asymptomatic VTE

Dentali F et al. Thromb Res 2010; 125: S166-S191

Prognostic Relevance of i-PE

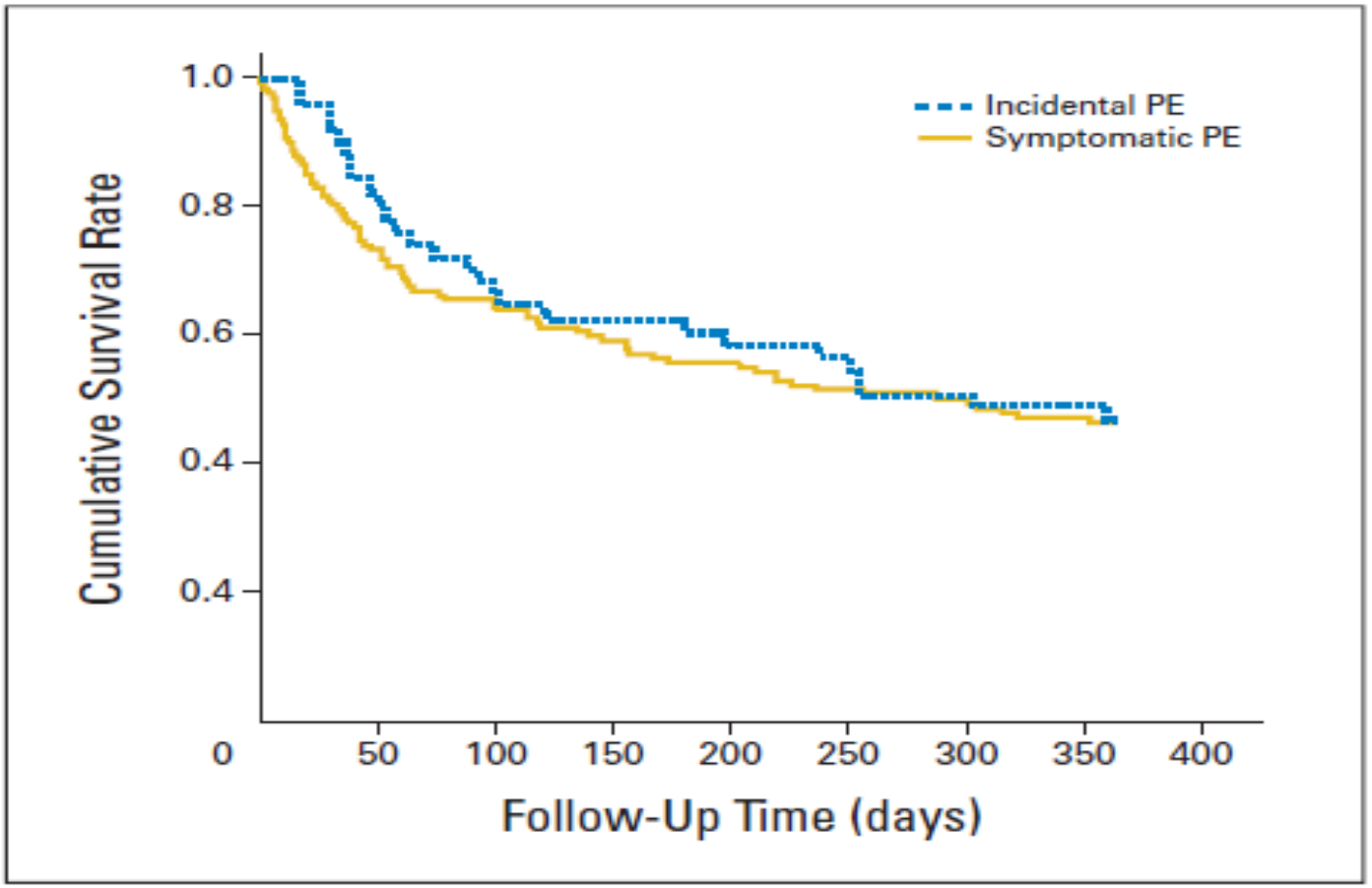
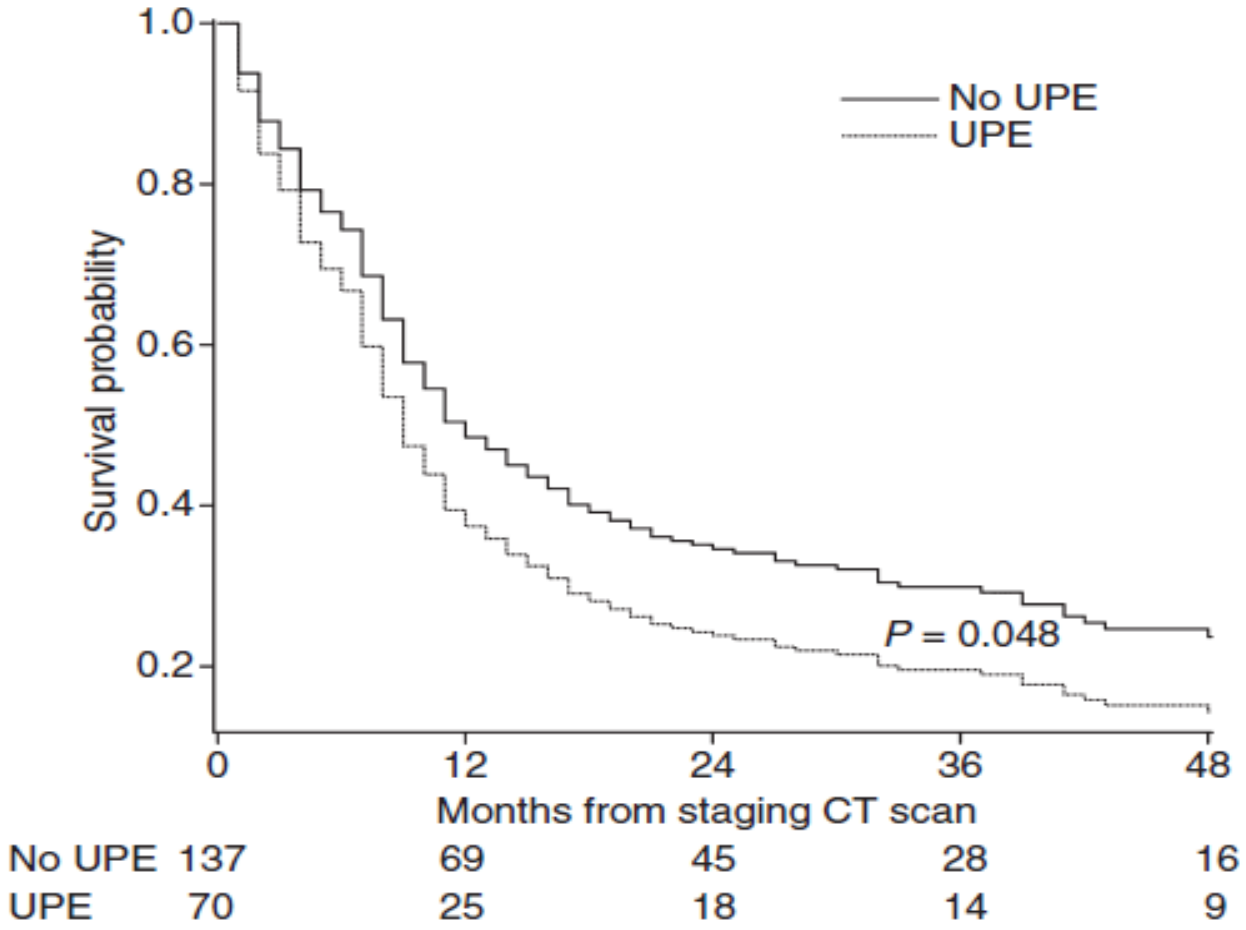


Fig 2. Kaplan-Meier cumulative survival curve until overall death for patients with cancer with incidental versus symptomatic pulmonary embolism (PE; $P = .70$).

den Exter et al JCO 2011; 29:2405-2409.

Prognostic Relevance of incidental PE.



O'Connell et al JTH, 2011 9: 305–311

To treat or not to treat?

- Untreated i-PE is more lethal than treated
  - From a cohort of 926 patients 53 were left untreated [1]
    - 47% 6 month mortality vs. 28% (VKA) & 37% (LMWH)
  - 113 iPEs (Lung Cancer) 50% were treated at Clinicians discretion –some left untreated-no difference in stage PS, or treatment response [2]
    - 30.9 months median survival (treated) Vs. 6.1 months (untreated)
      - HR 4.1 (95% CI 2.3-7.6)

[1]van der Hulle et al JTH 2016; [2]Sun et al Lung Cancer 2010

Long-term Treatment of Patients With PE
ACCP Guidance (2011)

In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B).

Kearon et al Chest 2011

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Kearon et al Chest 2011

So where lies the controversy?

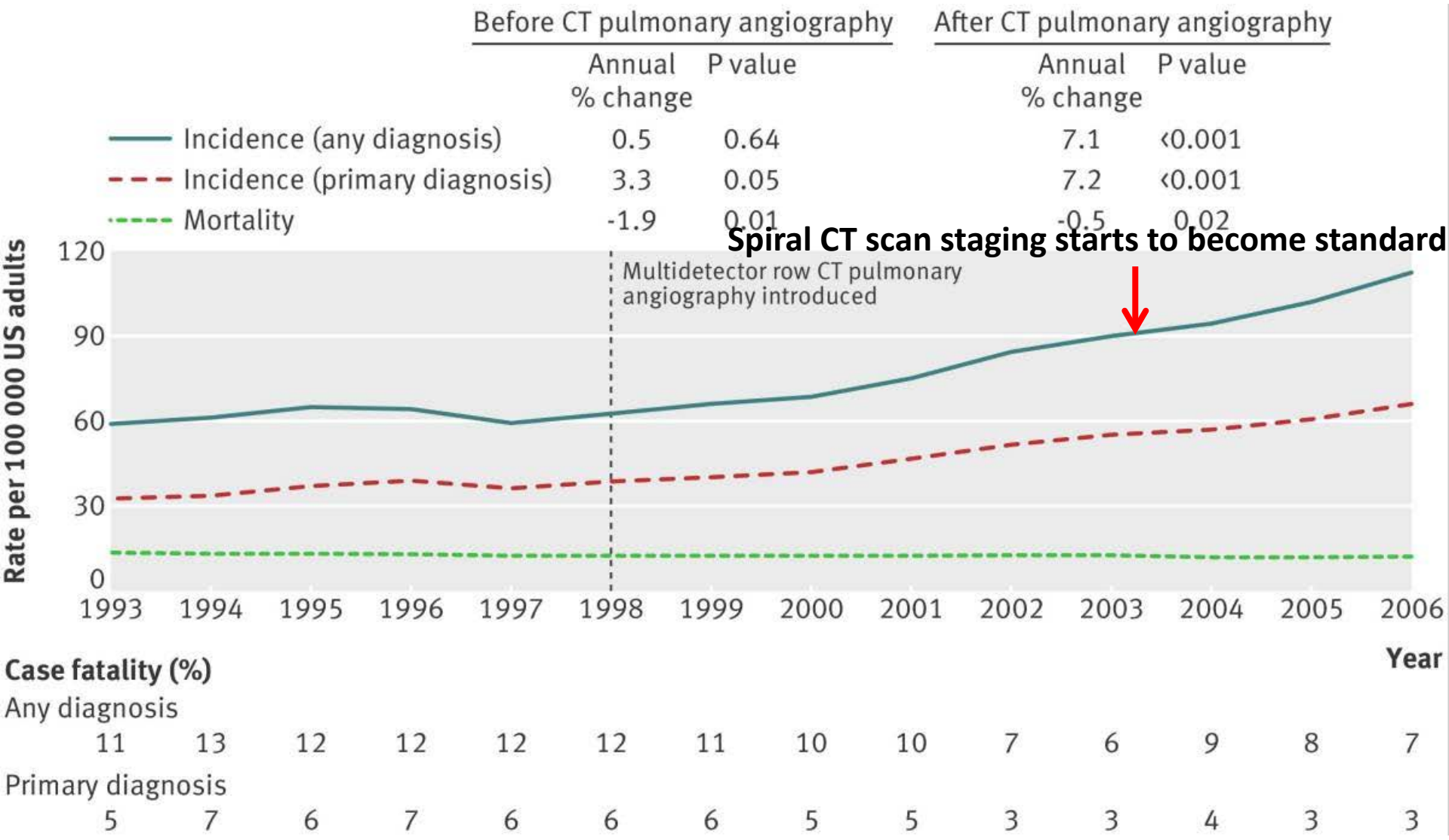
SSPE (Sub-segmental PE)

Example of an SSPE

SSPE Controversy

- Much of the data we rely on was generated when V/Q scans were standard of care
  - V/Q scans have very low sensitivity in SSPE
  - Likely SSPE was in the low probability for PE classification
    - No obvious adverse outcomes[1]
- Anecdotally untreated SSPE in the non-Cancer setting does not seem to have adverse outcomes[2]
- Epidemiological data in the NON cancer setting suggest that despite more PE being found mortality remains unchanged

[1]Anderson et al JAMA 2007;298:2743-53
[2]Donato AA et al Thromb Res 2010;126:e266-70.



Weiner et al BMJ 2013 Jul 2;347:f3368

	True Increase in Disease	Effective test	Overdiagnosis
Scenario	**Increase in risk factors results in more pulmonary emboli, with no change in disease severity.**	**More sensitive test detects more pulmonary emboli, and new cases benefit from treatment -> fewer deaths.**	**More sensitive test detects more pulmonary emboli, and new cases do not benefit from treatment (mild disease).**
Apparent Incidence Diagnosed PE / US population	Increased	Increased	Increased
Mortality Fatal PE / US population	Increased	Decreased	No change
Case-Fatality Fatal PE / Diagnosed PE	No change	Decreased	Decreased

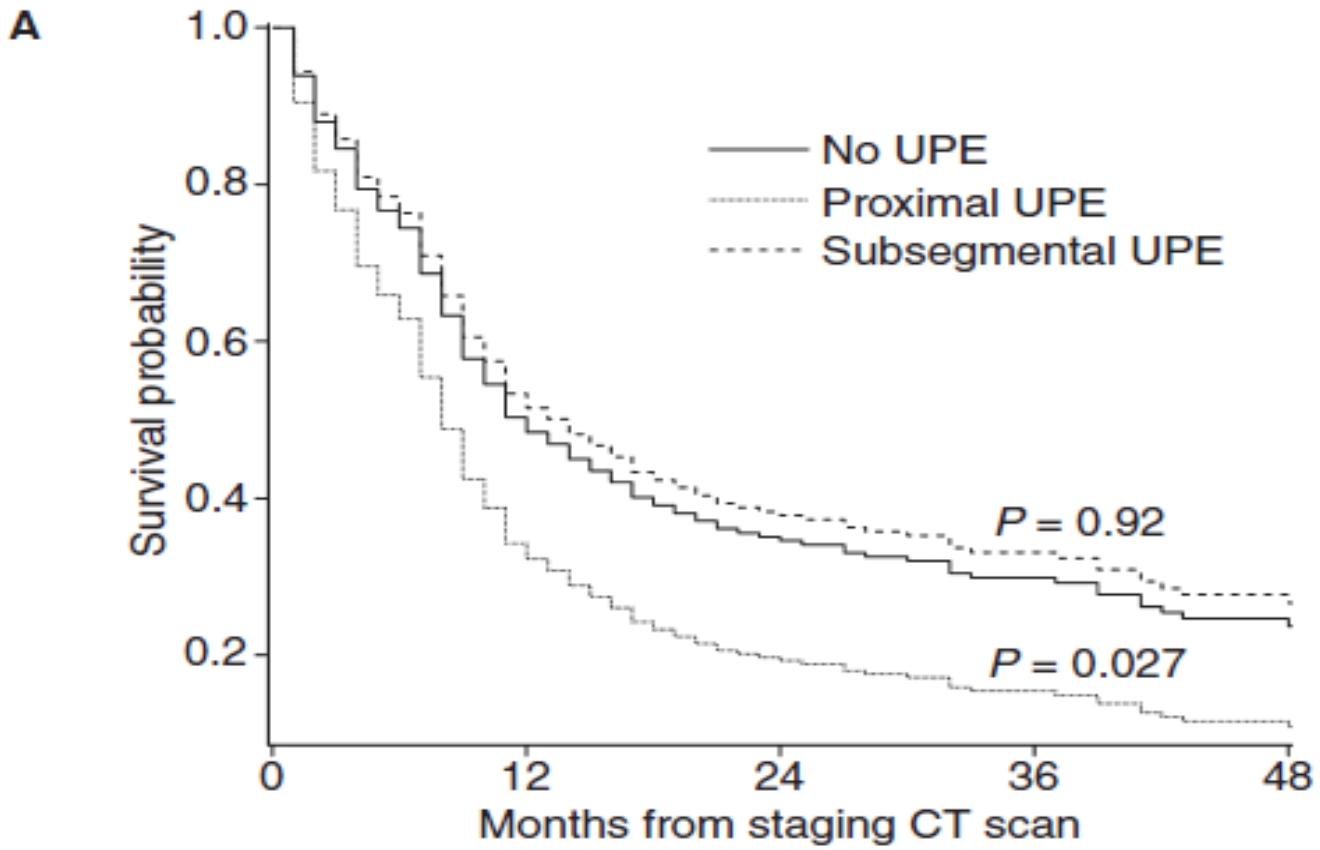
Weiner et al Arch Intern Med. 2011;171: 831–7

i-SSPE in Cancer

Author	UPE	SSPE	Reference
Shinagare et al	202	13 (6.4%)	**Cancer. 2011 15;117:3860-6**
Maraveyas et al	155	14 (9%)	**Thrombosis Res 129: S183**
Sun et al	113	0 (0%)	**Lung Cancer 2010;69:330–6.**
O'Connell et al	70	17 (24%)	**JTH, 2011 9: 305–311**
Sahut D'Izarn et al	66	10 (15.2%)	**JTH, 2012;10:2032-8.**
Den Exter et al	45	4 (8%)	**JCO 2011 29:2405-9**
Browne et al	18	3 (16.7%)	**J Thorac Oncol 2010;5:798–803.**
	669	**61 (9.1%)**	

Does i-SSPE have a survival impact in Cancer?

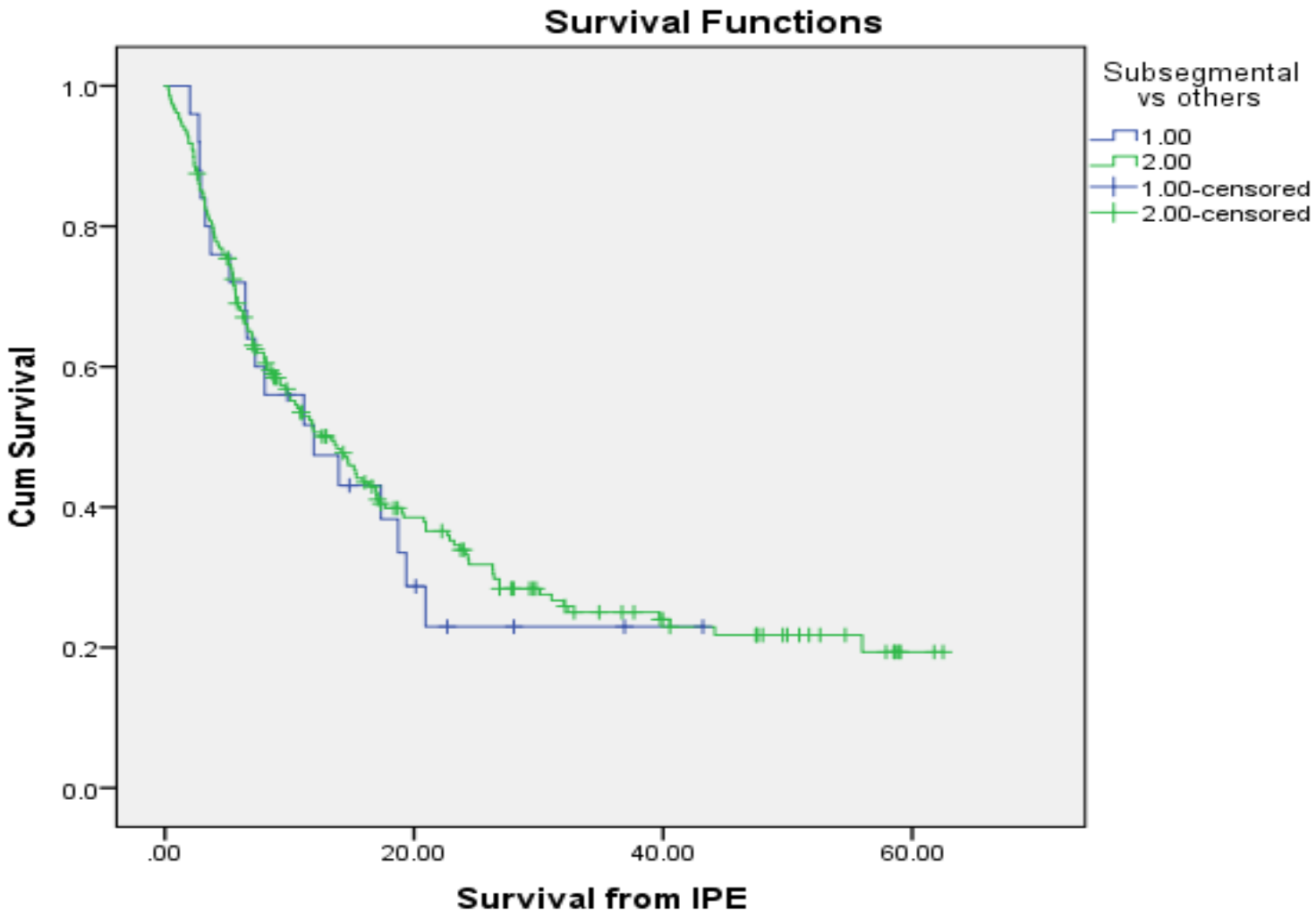
The incidental SSPE in Cancer



No UPE	137	69	45	28	16
Proximal UPE	53	16	12	10	5
Subsegmental UPE	17	9	6	4	4

O'Connel et al JTH, 2011 9: 305–311

The incidental SSPE in Cancer



Bozas et al unpublished

The 'symptomatic' SSPE

(Not a cancer patient study)

- CTPA for 3728 patients with clinically suspected PE
- PE confirmed in 748 patients,
  - of whom116 (16%) had SSPE
  - Active malignancy, 21 (18.1%) SSPE and 113 (17.9) had Proximal PE
- 'Proximal' PE Vs SSPE
  - 3-month risk of recurrent VTE (3.6%vs 2.5%; P= .42), and mortality (10.7%vs 6.5%; P=.17)
  - SSPE were at an increased risk of VTE during follow-up (hazard ratio: **3.8**; 95% CI: 1.3-11.1).

den Exter et al Blood 2013; 122: 1144-1149

Symptomatic Vs asymptomatic i-PE

(Cancer Patients)

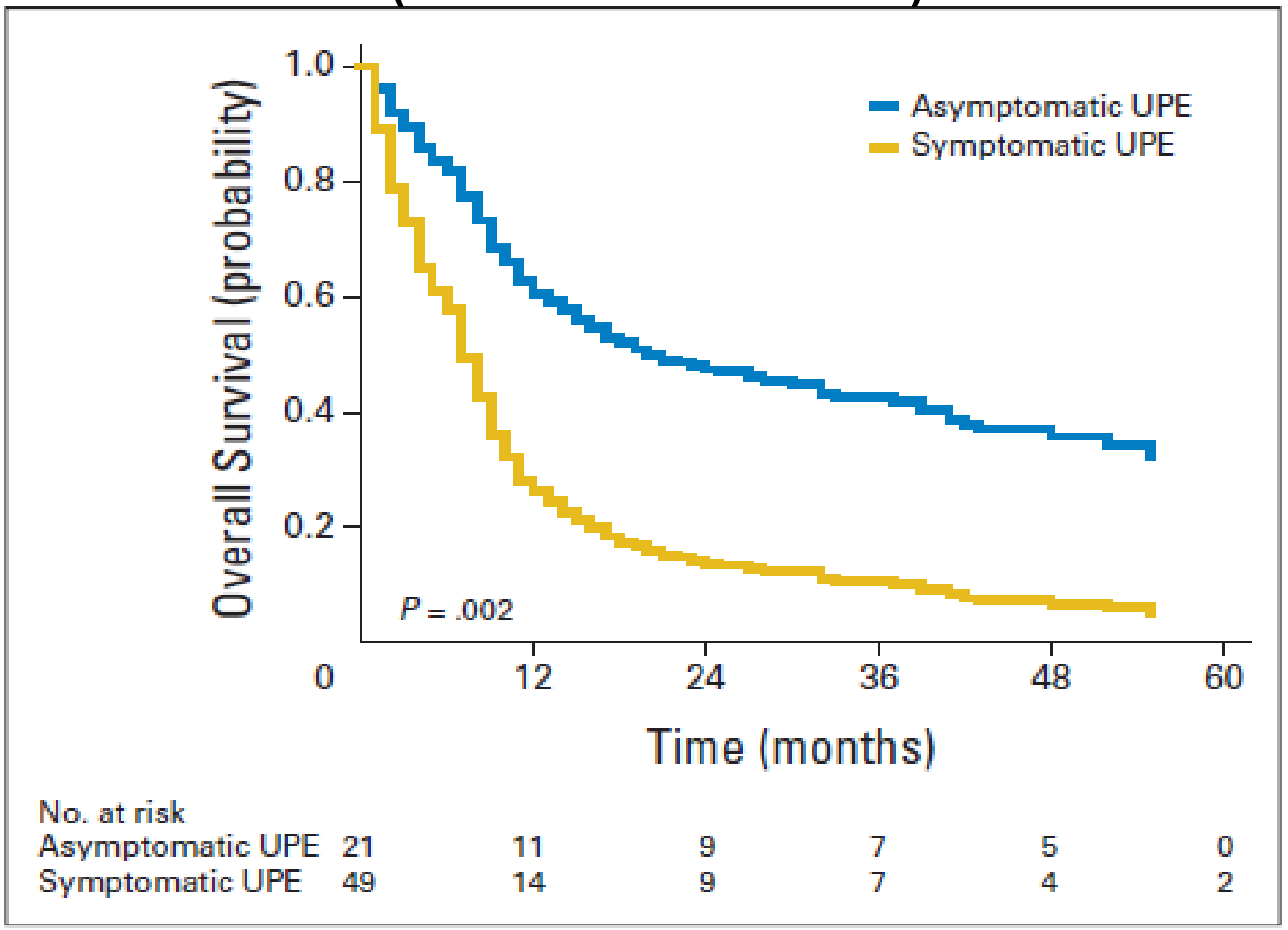
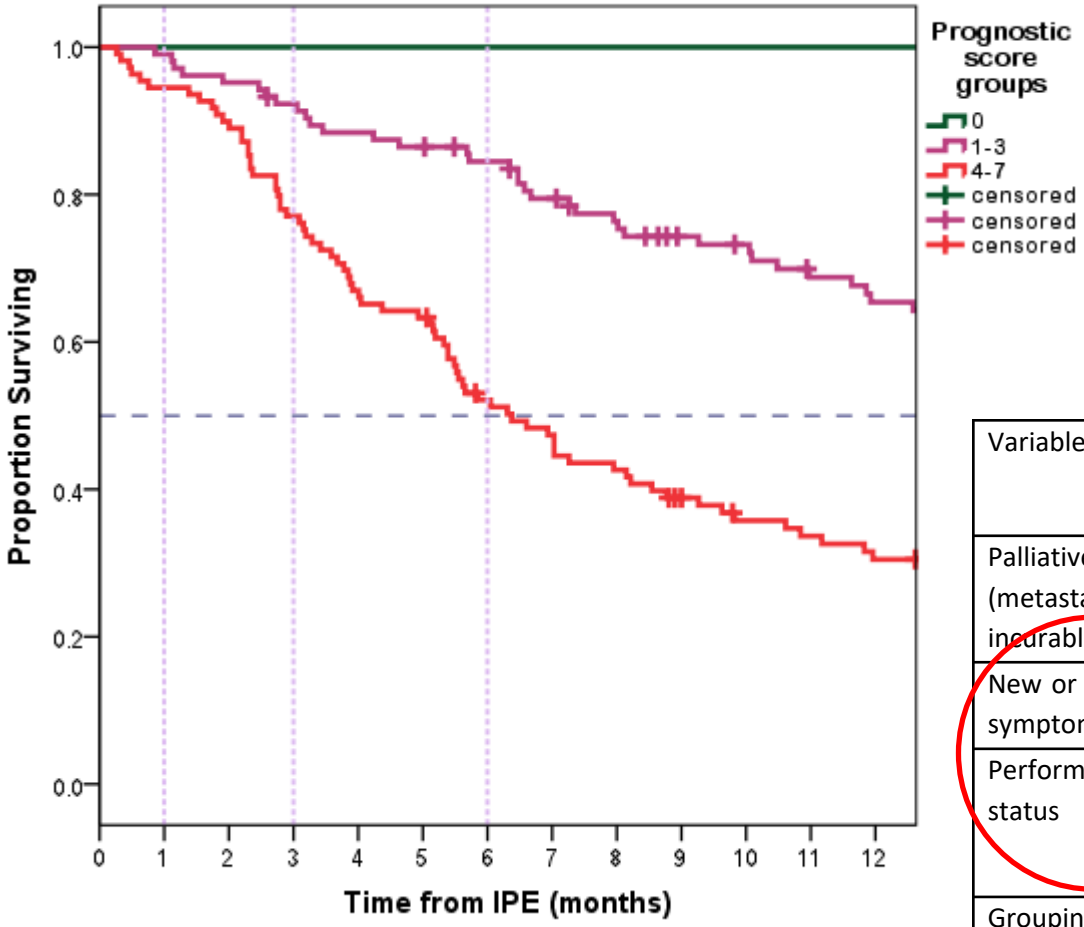


Fig 1. Kaplan-Meier curve for overall survival of patients with asymptomatic versus symptomatic unsuspected pulmonary emboli (UPE).

O'Connel et al JCO, 2011; 4208-4209

The Hull I-PE Prognostic Index



Variable	Categories	P	Points assigned
Palliative setting (metastatic or incurable disease)	Yes No	<.001	2 0
New or worsening symptoms	Yes No	.010	1 0
Performance status	0 1/2 3/4	<.001 <.001	0 3 4
Grouping	**Low Risk: 0, intermediate risk: 1-3 high risk: >3**		

Bozas et al unpublished

Clinician survey of SSPE

- **Cancer, Chest and palliative care physicians**
  - 154 physicians responded.
  - In the **adjuvant setting,** oncologists were more likely to immediately anticoagulate for a single **asymptomatic** SSPE than palliative care physicians or chest physicians (84 vs 46 vs 56 %, respectively, p = 0.001).
  - In the **metastatic setting** the differences were smaller (89 vs 69 vs 76 %, respectively, p = 0.057)

Lim et al (2015) Thromb Thrombolysis. 37-41

Clinician survey of SSPE

- In **the adjuvant setting** the percentage of surveyed physicians who would initiate anticoagulation immediately **in the presence of new onset dyspnea and fatigue** would rise to 93% (95%CI:88%-97%) for a single-site SSPE.
- **In the metastatic setting** this same percentage was 94% (95%CI:89%-97%).

Lim et al (2015) Thromb Thrombolysis. 37-41

Guideline Recommendations ACCP 2016

- In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C), and (ii) **high risk for recurrent VTE (see text),** we suggest anticoagulation over clinical surveillance (Grade 2C).
  - **(Text)** Patients hospitalized or have reduced mobility for another reason; **have active cancer (particularly if metastatic or being treated with chemotherapy);** or have no reversible risk factor for VTE such as recent surgery.

Kearon et al CHEST 2016

Conclusions

- Avoid terms like ‘asymptomatic’ or ‘silent’ when making the **radiological** diagnosis
  - Incidental, Unsuspected
- However symptomatic Vs. non symptomatic characterization is rational for further management.
- In the presence of a cancer diagnosis, treatment etc guidelines recommend anticoagulation of an IPE.
  - Some evidence exists for worse outcomes of untreated IPE patients

Conclusions

- If the patient has an SSPE
  - In the presence of active Cancer or Cancer treatment as a provoking factor anticoagulation is recommended (ACCP Grade 2 C)
  - In the **true absence of symptoms** and non-active cancer and or treatment > 6 months (e.g. Cancer surveillance period) one can consider clinical surveillance of the SSPE patient over treatment (ACCP Grade 2 C) after negative bilateral leg Doppler.
  - In the presence of **new symptoms however** consider anticoagulation (dan Exeter Blood 2013)

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    - **'...patients told to return for re-evaluation if symptoms persist or worsen'.**
  - In the presence of **new symptoms however** consider anticoagulation (dan Exeter Blood 2013)

*Standard for clinical surveillance?

- NCT01455818 (OTTAWA, Carrier et al)
  - Weekly phone call for the first 4 weeks then monthly **up to 90 days**.
  - Questionnaire used to elicit signs and symptoms of recurrent VTE during the phone calls
  - Symptom resolution not formally assessed
  - Patients with suspected recurrent VTE are seen urgently in clinic.

Thank you