Can oesophageal cancer patients avoid surgery?

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I hope so……

If we select with caution…

What do patients say?

- NACT + Surgery (2 years on): “I may not be eating as well as I want to but am glad that my tumour is out and I am cancer free after 2 years.”
- NACT + Surgery(1.5 year on): “I wish I knew that my eating and my general life will be this miserable after the operation”.
- dCRT (SCOPE2, 4 years on): “I am glad that I had opted for radiotherapy as my treatment”.
- dCRT (SCOPE 2, 2 years on): I may be cancer free but I still can’t eat steak and chips!”.

What has been achieved so far with pre-op non-surgical treatment and surgery?

CROSS (41.4Gy in 23 fractions)

Parameter	41.4 Gy and paclitaxel/carbo-platin followed by surgery	Surgery alone	p value
Subjects, n	178	188	>0.05
Adeno/SCC	134/41	141/43	
Complete resection (R0), %	92	69	<0.001
pCR, %	29	–	
ypN+, %	31	75	<0.001
Postoperative complications, n			
Pulmonary	46	44	
Anastomotic leakage	22	30	
Death (in hospital/30 days)	4/2	4/3	
Median OS, months	49.4	24	0.003

Adeno = Adenocarcinoma; SCC = squamous cell carcinoma; pCR = pathological complete response; ypN+ = lymph node status; OS = overall survival.

NEOSCOPE (RT dose 45Gy in 25 fractions)
Mandard Tumour Regression Grade

	OxCapRT (n=42)		CarPacRT (n=43)	
	n	**%**	**n**	**%**
1 (pCR)	5	11.9	12	27.9
2	13	31.0	16	37.2
3	13	31.0	10	23.3
4	4	9.5	3	7.0
5	0	0.0	0	0.0
Missing TRG data	1	2.4	0	0.0
No surgery	6	14.3	2	4.7

Of those having surgery, pCR was 5/36 (13.9%) in OxCapRT and 12/41 (29.3%) in CarPacRT

10 of first 38 patients in the CarPacRT arm attained pCR, thereby meeting pre-specified criteria of success

Slide courtesy: Prof. Somnath Mukherjee

Neo-AEGIS (RT dose 41.4 in 23 fractions)

	Arm A MAGIC/FLOT	Arm B CROSS
R0 (negative margins)	**82%**	**95%**
ypN0	**44.5%**	**60.1%**
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	**5%**	**16%**
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III<V	23.6%	22%

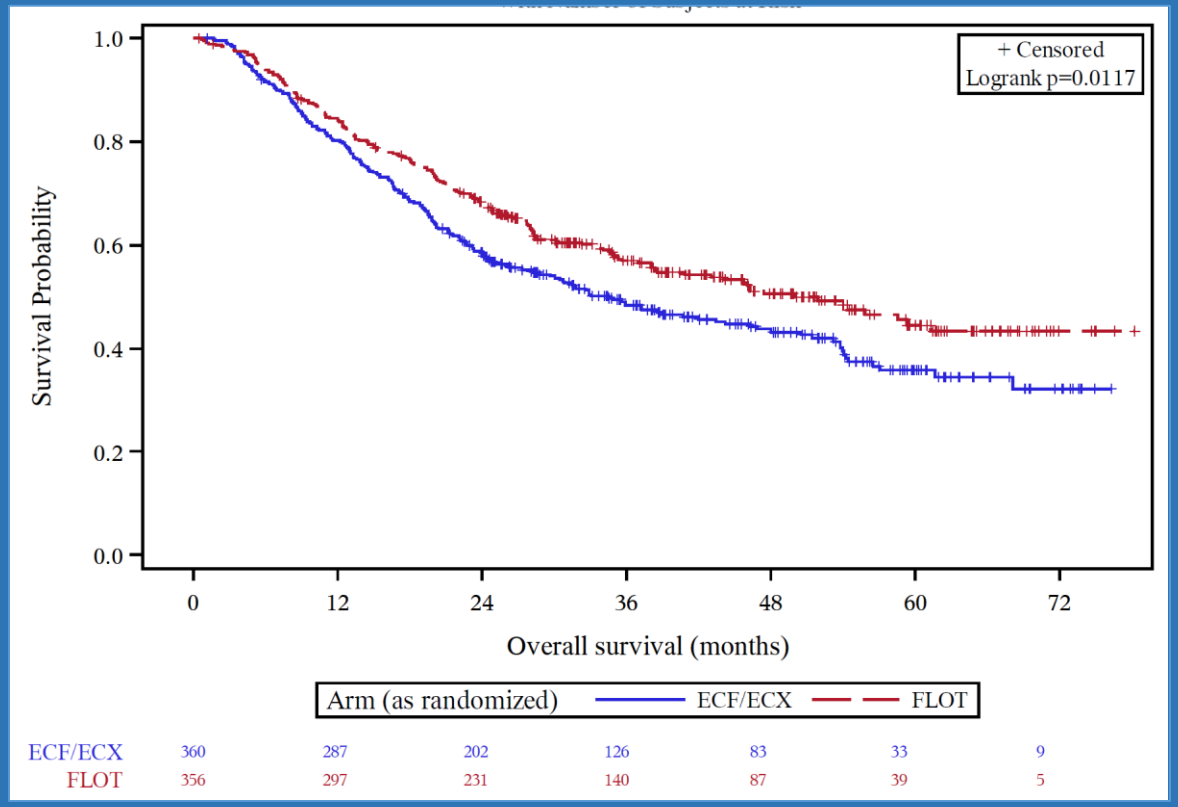
FLOT

	ECF/ECX (n=137)	95% CI	FLOT (n=128)	95% CI	p value*
Complete (TRG 1a)†	8 (6%)	2·8–11·3%	20 (16%)	10·3–23·0%	0·02
Subtotal (TRG 1b)	23 (17%)	11·4–24·0%	27 (21%)	14·9–29·0%	..
Complete or subtotal (TRG 1a/b)	31 (23%)	16·4–30·4%	47 (37%)	28·9–45·4%	0·02
Partial (TRG 2)	28 (20%)	14·5–28·0%	23 (18%)	12·2–25·6%	..
Minimal or none (TRG 3)	52 (38%)	30·3–46·3%	49 (38%)	30·3–46·9%	..
No surgery	26 (19%)	13·2–26·4%	9 (7%)	3·6–13·0%	..

Data are n (%). ITT=intention-to-treat. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. TRG=tumour regression grade. *ECF/ECX compared with FLOT. †TRG1a was achieved in eight (7%) of 111 patients who had ECF/ECX and 20 (17%) of 119 patients who had FLOT (p=0·03) in the per-protocol population (resected patients).

Table 3: **Histopathological tumour regression in the modified ITT population according to Becker**

FLOT: Overall Survival



Median FU for surviving patients 43 months in both arms

	ECF/ECX	FLOT
mOS	35 months [27-46]	50 months [38-na]
HR	0.77 [0.63 - 0.94] p=0.012 (log rank)	

OS rate*	ECF/ECX	FLOT
2y	59%	68%
3y	48%	57%
5y	36%	45%

*projected OS rates

Survival in Surgical trials

- OEO2 (2009):Three-year survival by type of resection was R0 42.4%, R1 was 18.0%, and R2 was 8.6%.
- OEO5 (2017): Median survival was 23·4 months (95% CI 20·6-26·3) with CF and 26·1 months (22·5-29·7) with ECX (hazard ratio 0·90 (95% CI 0·77-1·05, p=0·19).
- CROSS (2015): SCC: 81.6mos vs 21.1; Adeno: 43.2 vs 27.1 mos
- FLOT: (44% Gastric ca): mOS: 50 vs 35(HR: 0.77); 3-year OS 57% vs 48%

What if surgery is omitted?

Definitive CRT: SCOPE1 (RT dose 50Gy in 25 fractions) SCC: Adeno- 75/25

39% over age 70
60% had stage III
47% were unsuitable for surgery due to local extent
16% were unsuitable due to co-morbidities
Introduction of high quality RTQA in UK OG practice

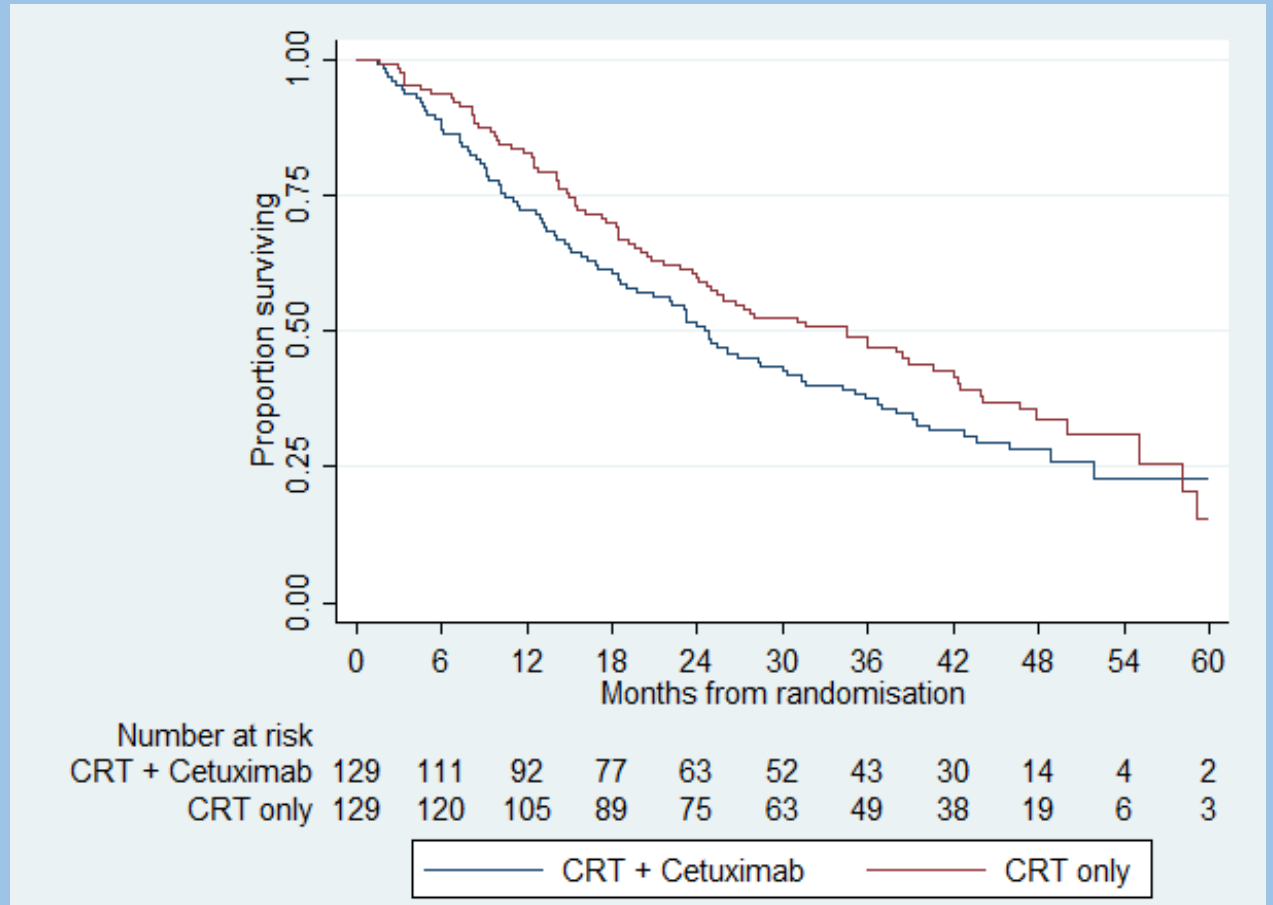
Overall survival

	Cetuximab (N=129)	No cetuximab (N=129)	Overall (N=258)
Median OS - months	**22.1**	**25.4**	**24.0**
2 year OS- %	**41.3**	**56.0**	**48.6**
Median PFS – months	**15.9**	**19.4**	**17.3**

	Median OS– months (95% CIs)
6 month Treatment Failure	**8.3 (6.7-12.5)**
6 month Treatment Failure Free	**26.7 (24.5-42.7)**

ie Stage 1 endpoint highly predictive of survival

Slide courtesy: Prof. T.Crosby



	dCRT	dCRT + C	HR, p
Median OS	35 (25-42)	25 (19-31)	(HR 1.25, p=0.137)
3 year OS	47% (38%-56%)	38% (29%-46%)	

Overall survival

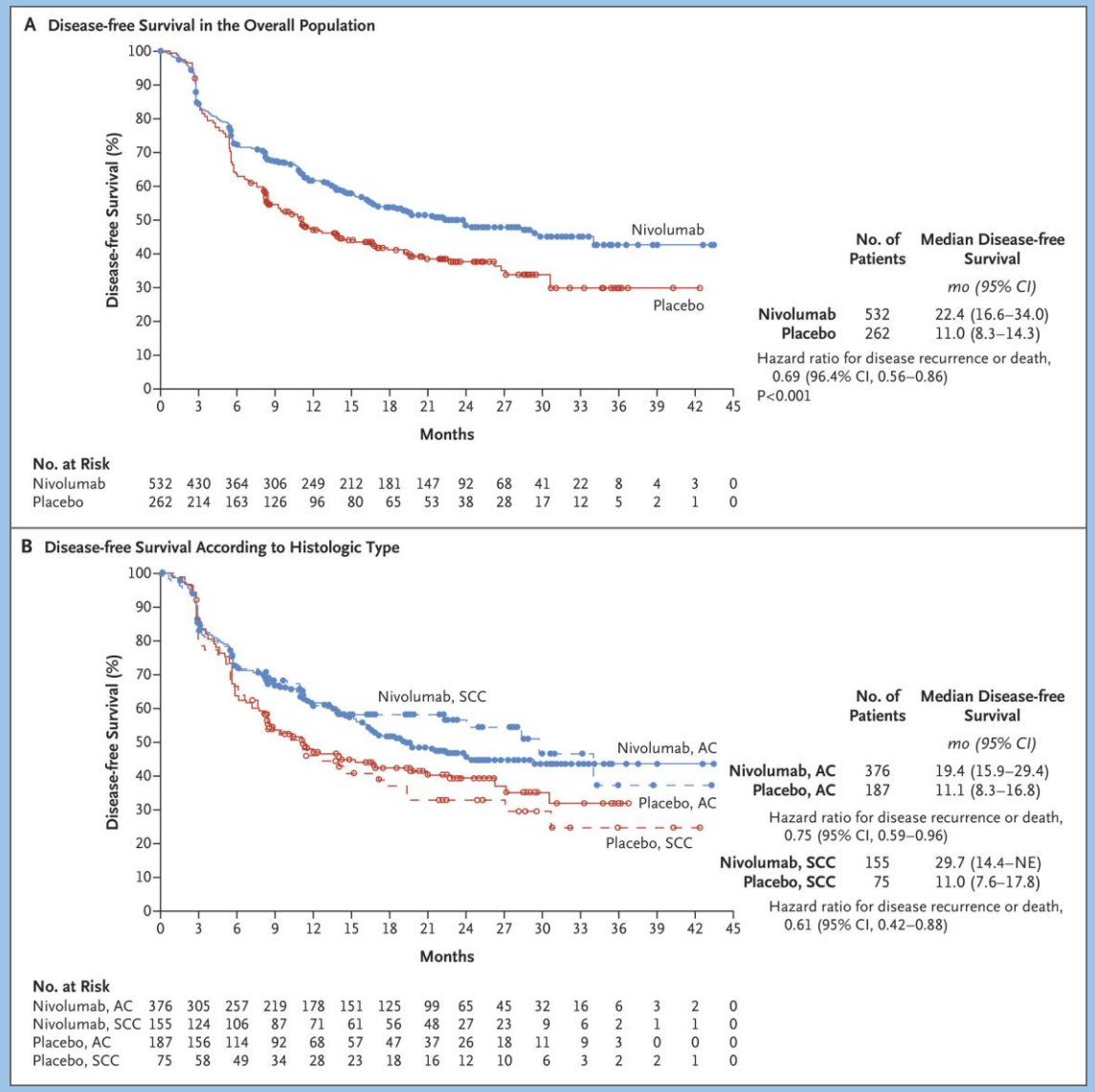
Slide courtesy: Prof. T.Crosby

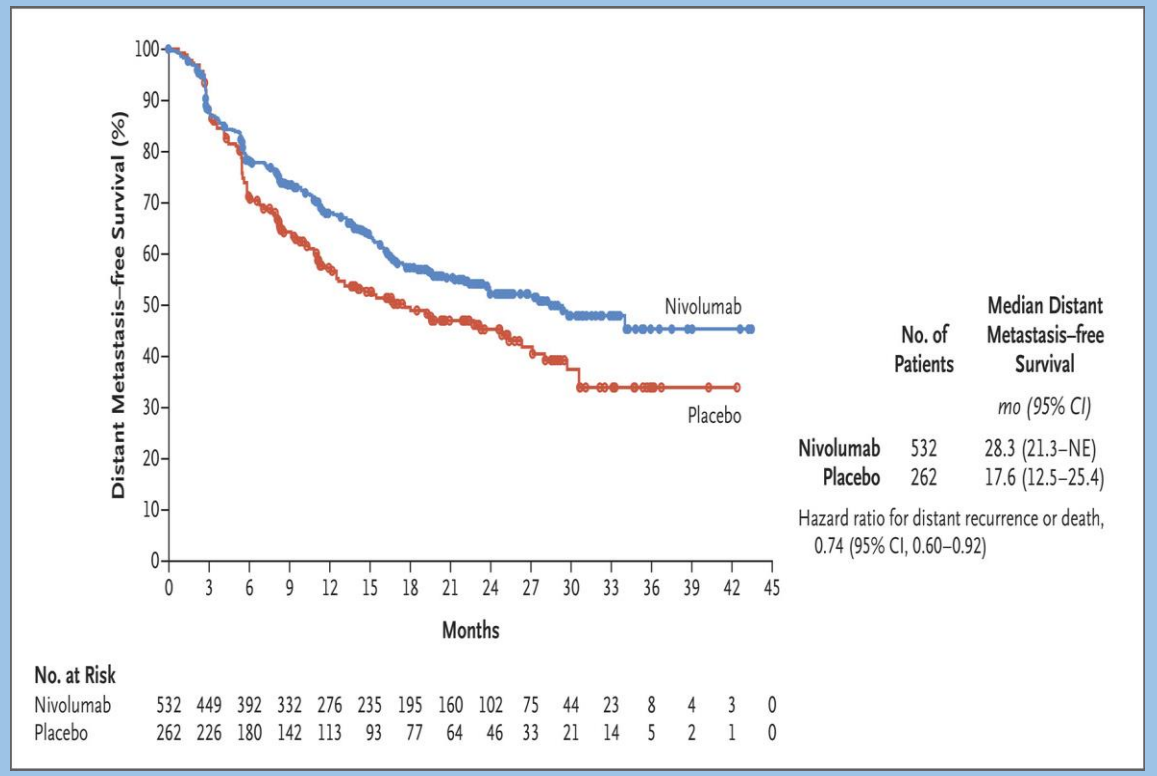
Patterns of Recurrence
SCOPE1

	Squamous cell						Adenocarcinoma/Undifferentiated					
	Infield		Outfield		Both		Infield		Outfield		Both	
	n	%	n	%	n	%	n	%	n	%	n	%
Loco-regional only	29	25.0	6	5.2	6	5.2	9	19.6	2	4.3	5	10.9
Loco-regional plus distant	11	9.5	4	3.4	5	4.3	4	8.7	3	6.5	2	4.3
Distant only			**55**	**47.4**					**21**	**45.7**		
Total	40	34.5	65	56.0	11	9.5	13	28.3	26	56.5	7	15.2

Slide courtesy: Prof. T.Crosby

CHECKMATE 577

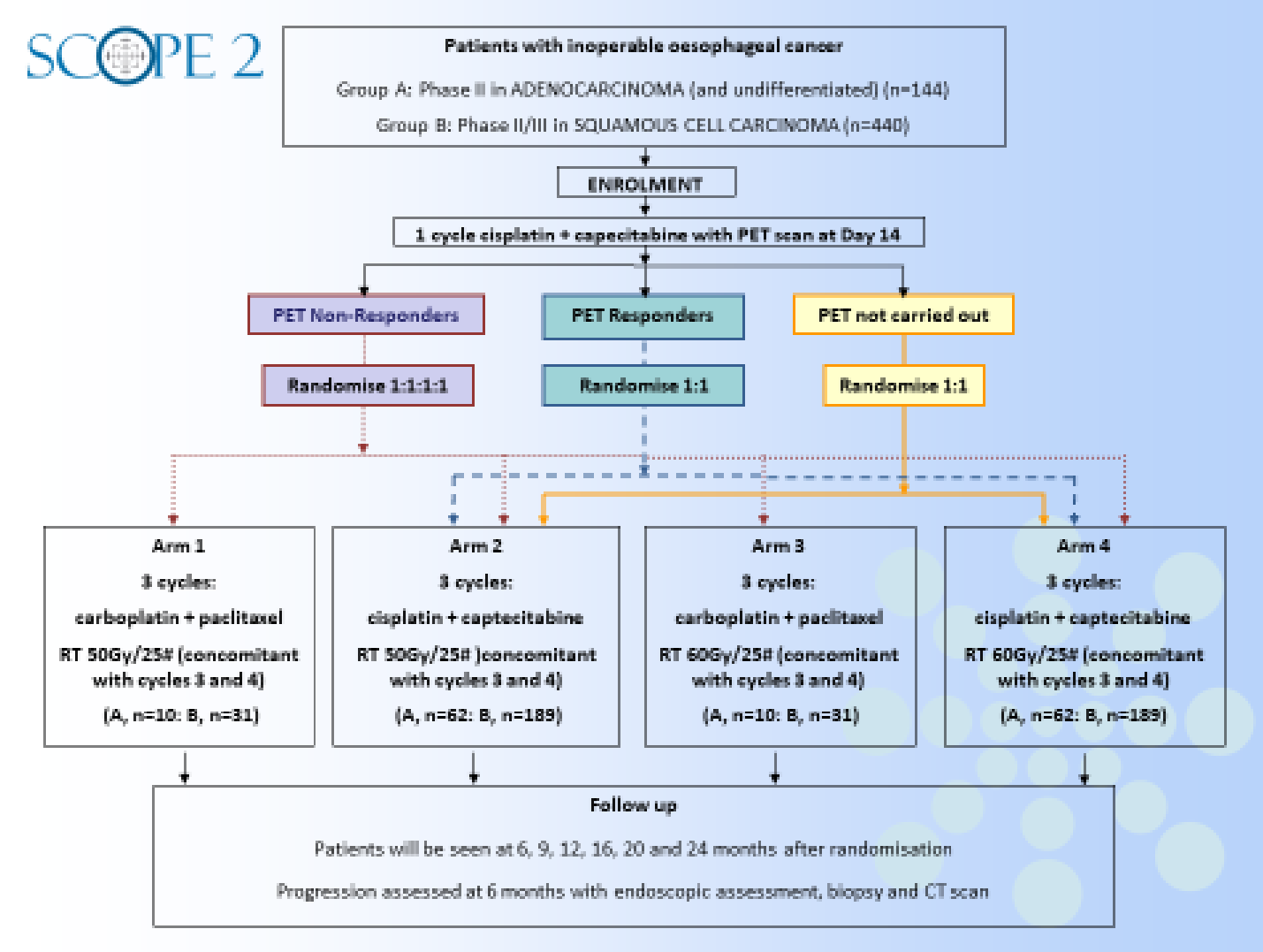




What are the barriers?

- Modest rate of complete response: Can we increase RT dose?
- **Difficulty in detecting true complete responders: Endoscopy/EUS/PET/Combination**
- **Robust follow-up protocol for early detection of local recurrence: Endoscopy/Cytosponge/ctDNA/PET/Combination**
- Recurrence within RT field: Insufficient dose
  Radio-resistant phenotype
- Distant Recurrence: Ineffective systemic treatment
  Chemo-resistant phenotype

Addressing RT related response and local control



Response assessment

Can we reliably predict pCR?

preSANO TRIAL

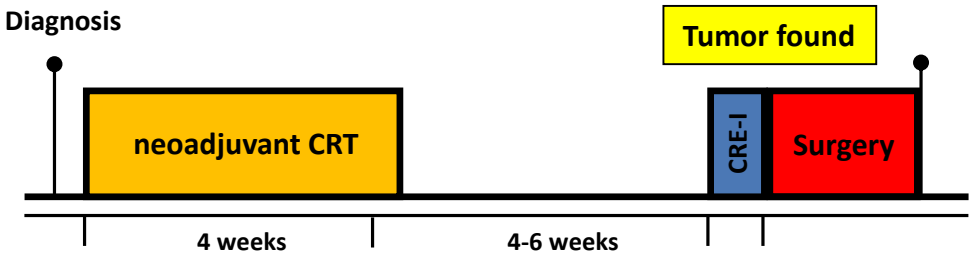
CRE-1:

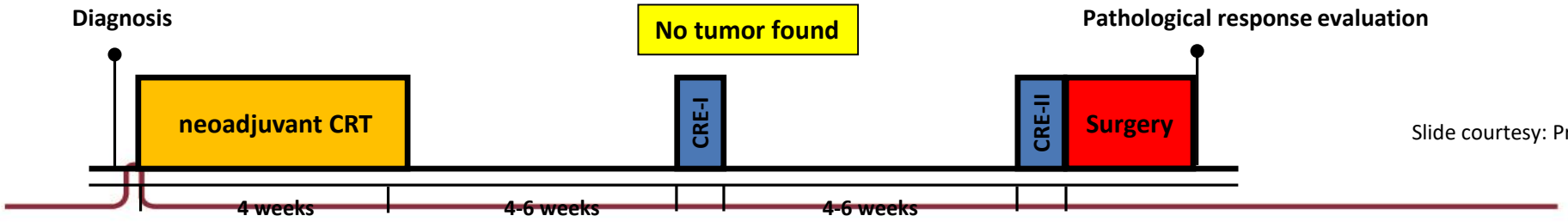
Endoscopy + Bx, EUS

PET-CT (if residual ds/strictured) → S

CRE-II:

1. PET-CT
2. -Endoscopic biopsies
   -EUS +
   -FNA <u>all</u> suspect nodes





Slide courtesy: Prof. Mukherjee

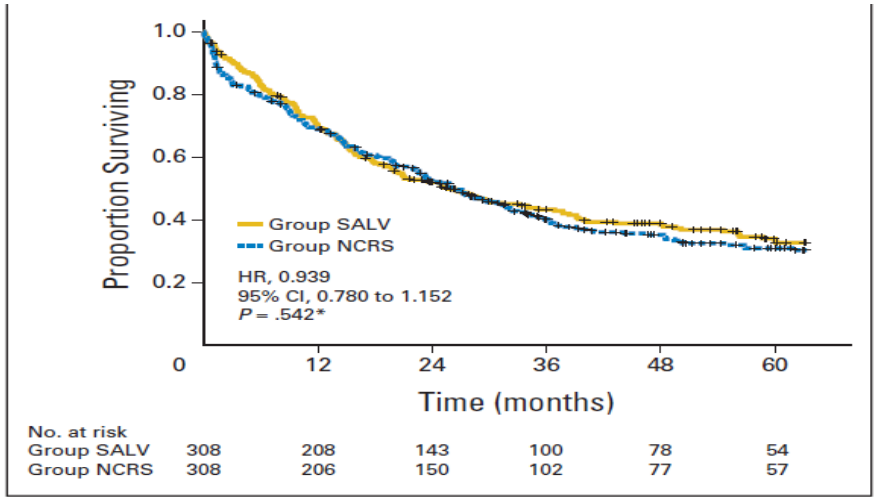
Pre-SANO (CROSS regimen + Surgery) Assessment at 4-6 weeks post CRT

- Eight of 26 TRG3 or TRG4 tumours (31% [95% CI 17-50]) were missed by endoscopy with regular biopsies and fine-needle aspiration.
- Four of 41 TRG3 or TRG4 tumours (10% [95% CI 4-23]) were missed with bite-on-bite biopsies and fine-needle aspiration.
- Endoscopic ultrasonography with maximum tumour thickness measurement missed TRG3 or TRG4 residual tumours in 11 of 39 patients (28% [95% CI 17-44]).
- PET-CT missed six of 41 TRG3 or TRG4 tumours (15% [95% CI 7-28]).
- PET-CT detected interval distant histologically proven metastases in 18 (9%) of 190 patients (one squamous cell carcinoma, 17 adenocarcinomas).
- **SANO results to look out for**

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option?

Sheraz Markar, Caroline Gronnier, Alain Duhamel, Arnaud Pasquer, Jérémie Théreaux, Mael Chalret du Rieu, Jérémie H. Lefevre, Kathleen Turner, Guillaume Luc, and Christophe Mariette



Retrospective, curative intended Surgery
30 centers
nCRT + planned Surgery: n= 540
dCRT + salvage Surgery: n= 308

High vs low volume center

In hospital mortality	6.3% vs. 16.2%, p=0.009
In hospital morbidity	58.8% vs. 80.9%, p=0.001

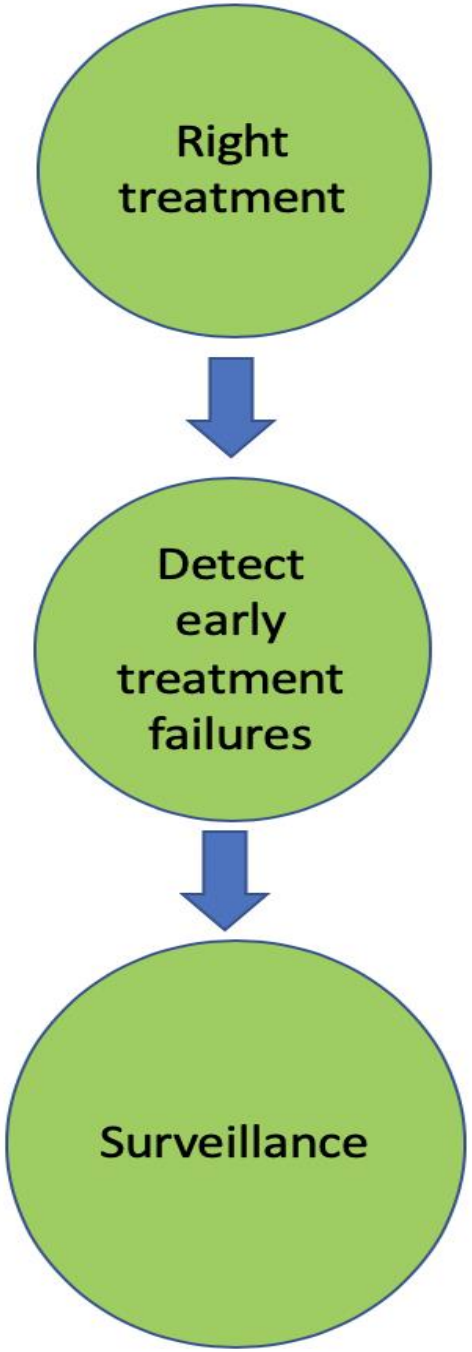
Dose of RT <55 Gy vs. ≥55 Gy

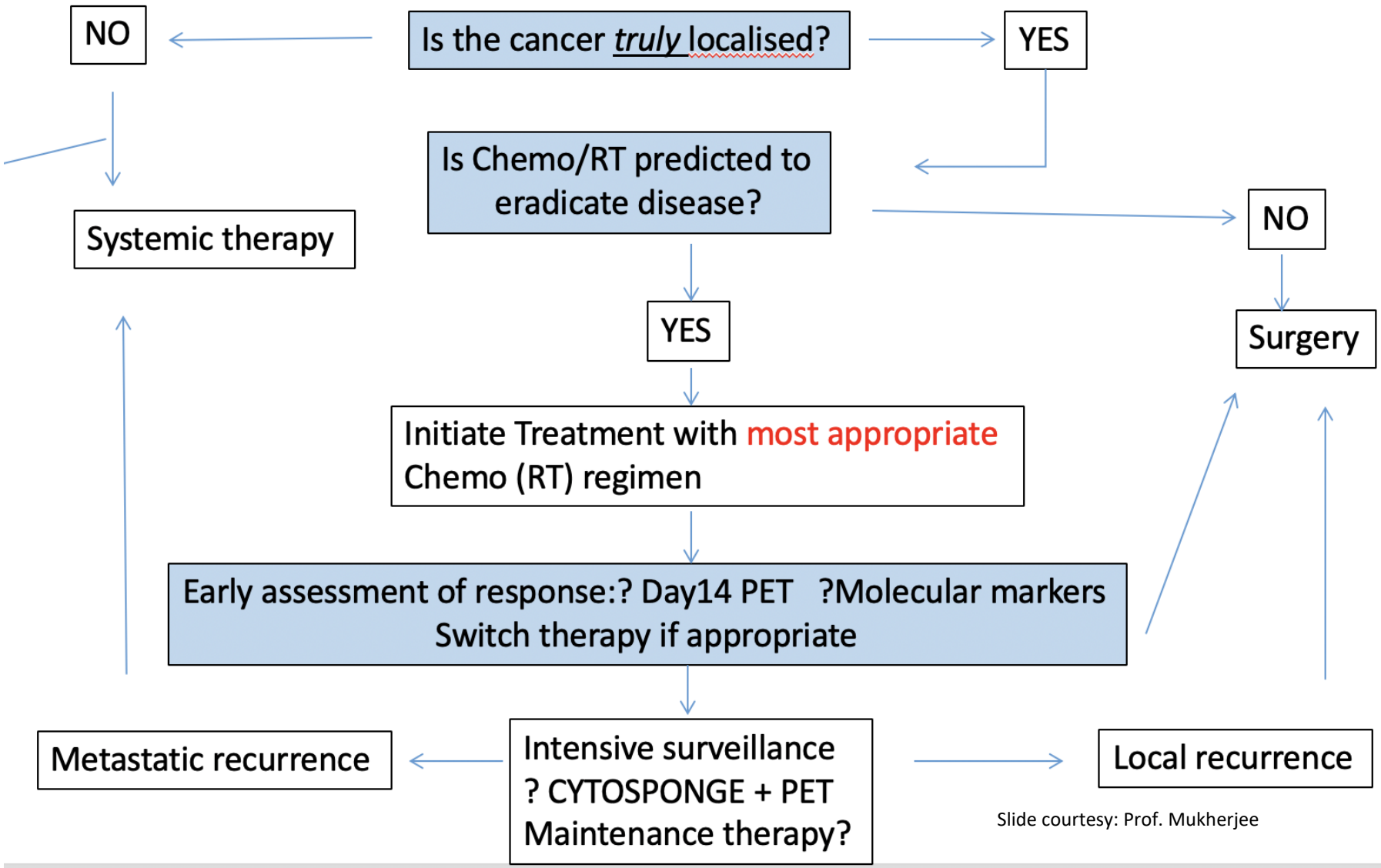
In hospital mortality	4.3% vs. 27.8%, p<0.001
In hospital morbidity	61.0% vs. 75.9%, p=0.039
AL	15% vs. 27.8%, p=0.023
SSI	16.1% vs. 29.6%, p=0.038
Pulm complications	40.2% vs. 55.6%, p=0.038

Slide courtesy: Prof. Mukherjee

J Clin Oncol, 2015

Future paradigm for localised cancer?

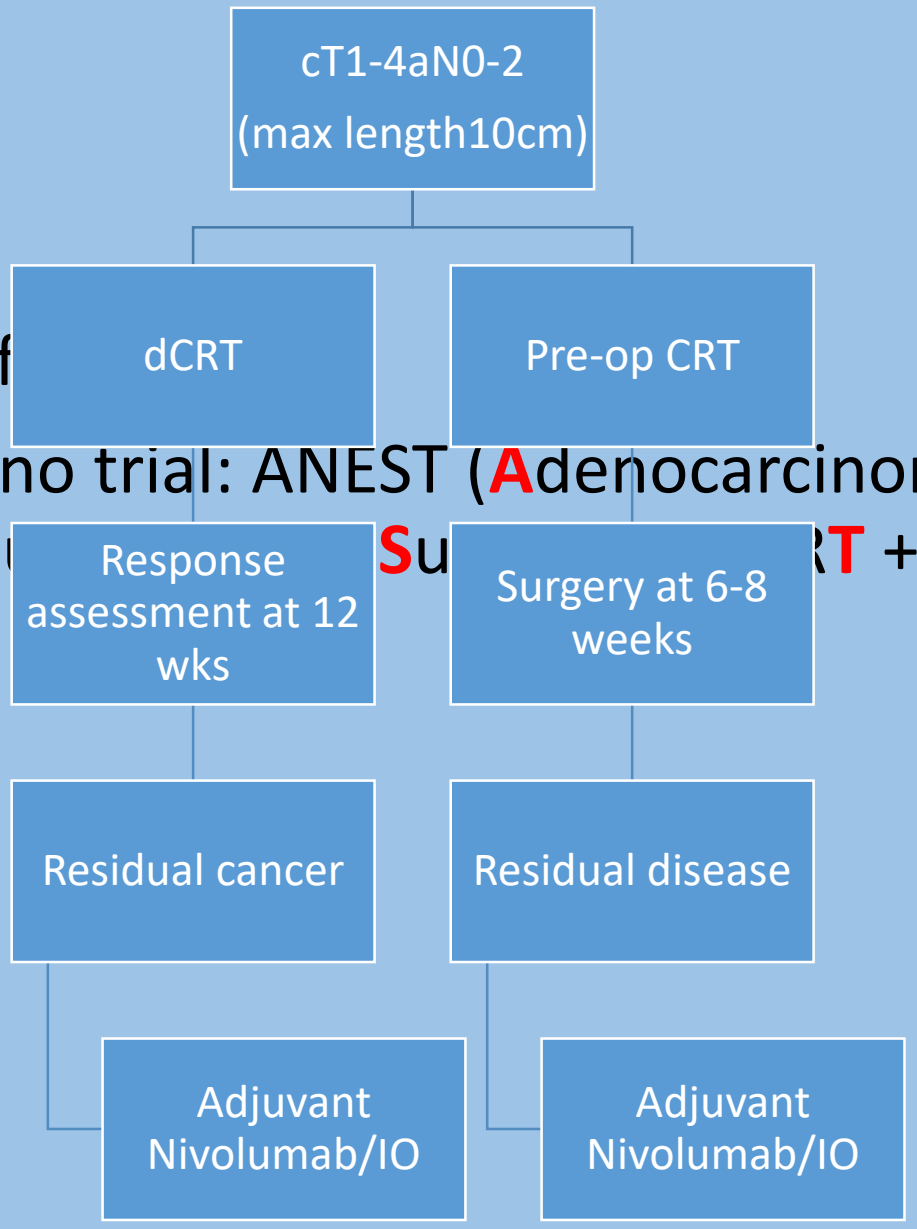




Slide courtesy: Prof. Mukherjee

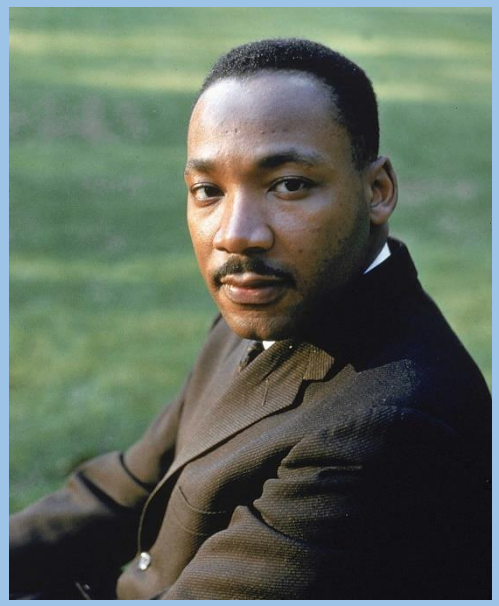
Future

- NEEDS Trial: Only f
- Can UK do an Adeno trial: ANEST (**A**denocarcinoma of esophagus treated by **NE**oadj **S**u **T** + Surveillance)trial



Dual Primary End-points: OS & QOL

I have a dream……..



Thank you

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