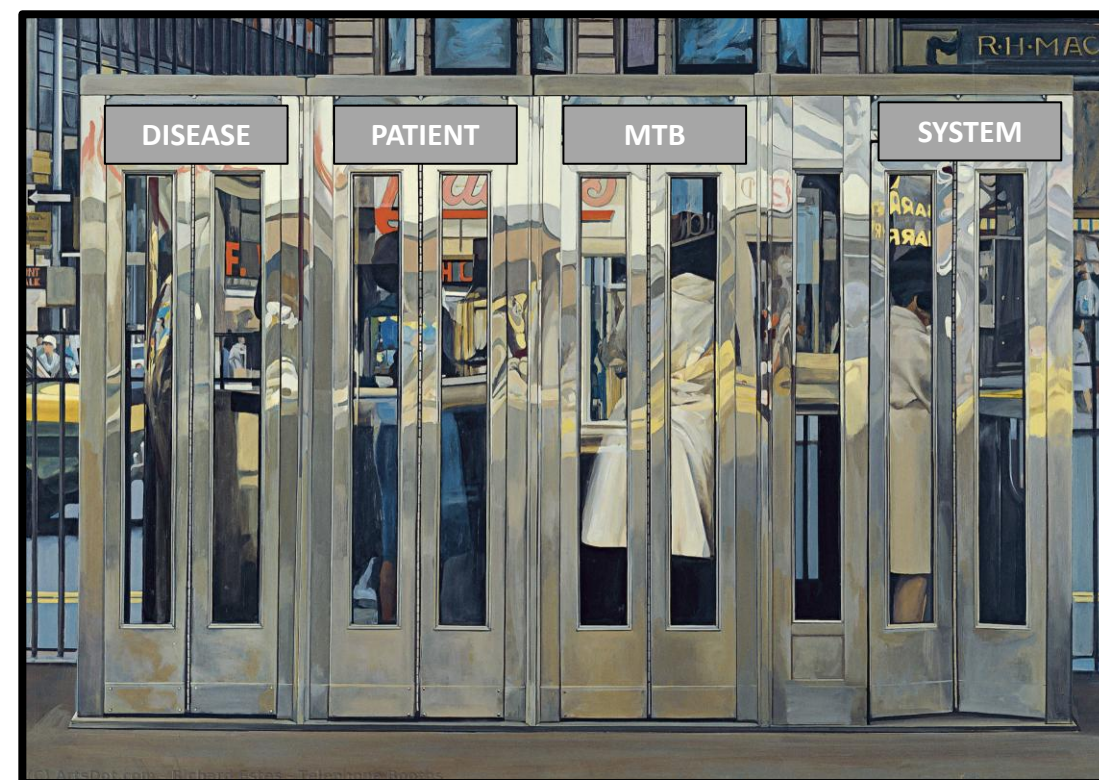




Optimal treatment of M0 esophageal squamous cell carcinoma: decisive factors in selection.

Javier Gallego Plazas, MD, PhD.
Medical Oncology Dpt.
Hospital Gral. Univ. Elche



Richard Estes, 1967

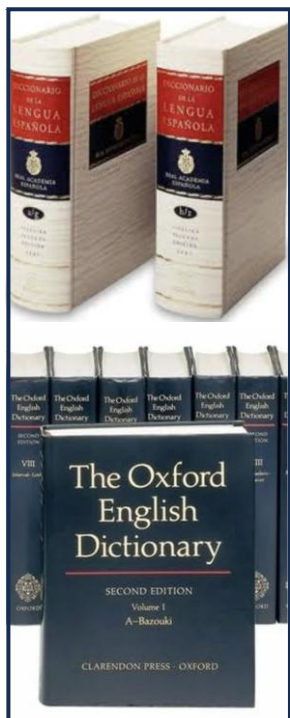
Financial conflicts of interest

- Employment: Generalitat Valenciana
- **Consultant or Advisory Role: BeOne, BMS, MSD.**
- Stock Ownership: None.
- Research Funding: None.
- Speaking: None.
- Grant support: None.
- Other: Virtual Congress: Amgen, Roche.



Optimal treatment of M0 esophageal squamous cell carcinoma:
decisive factors in selection.

Optimal treatment of M0 esophageal squamous cell carcinoma: decisive factors in selection.

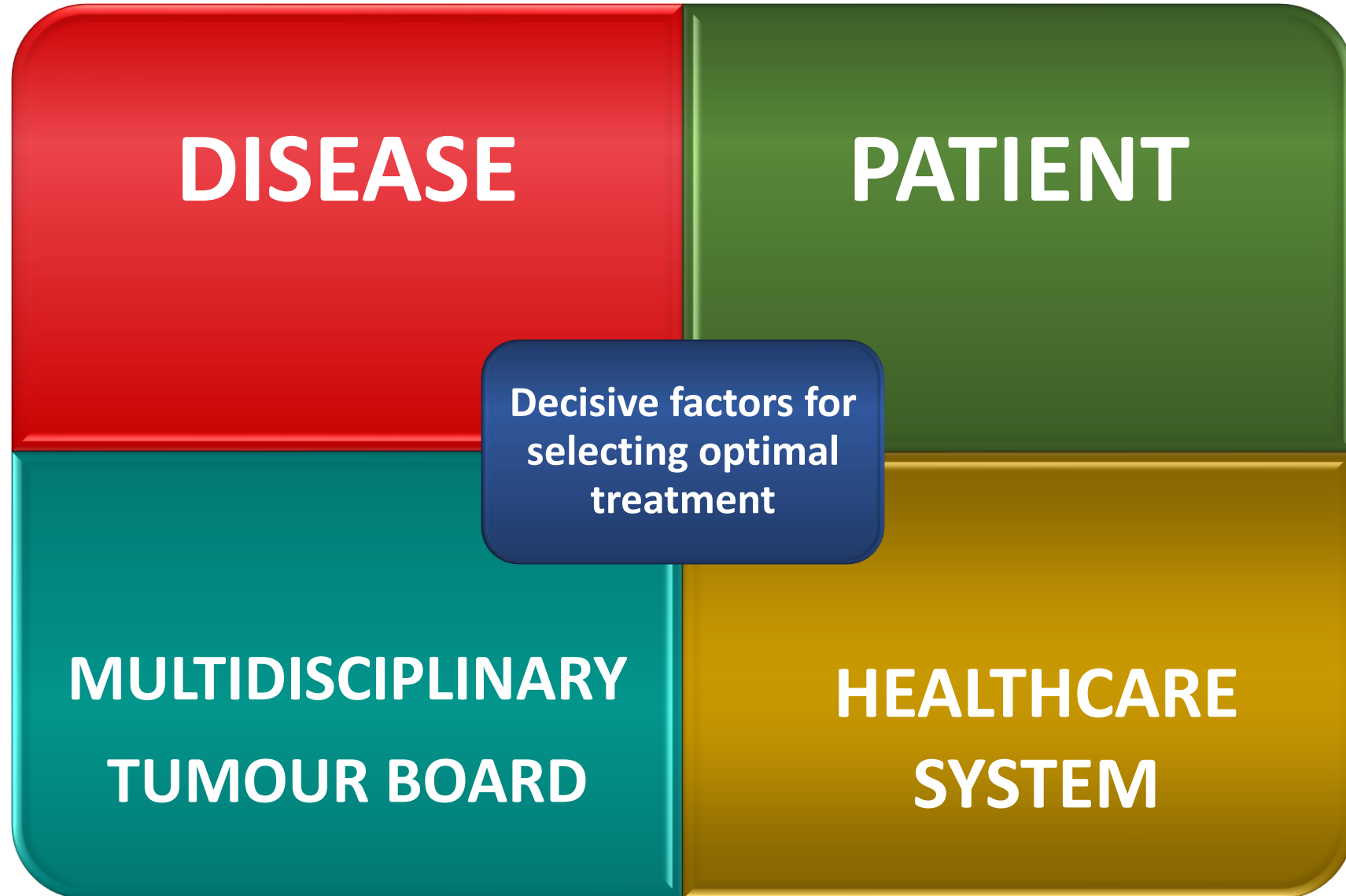


Optimal: the best possible, producing the best possible results.
In a particular situation or circumstance.

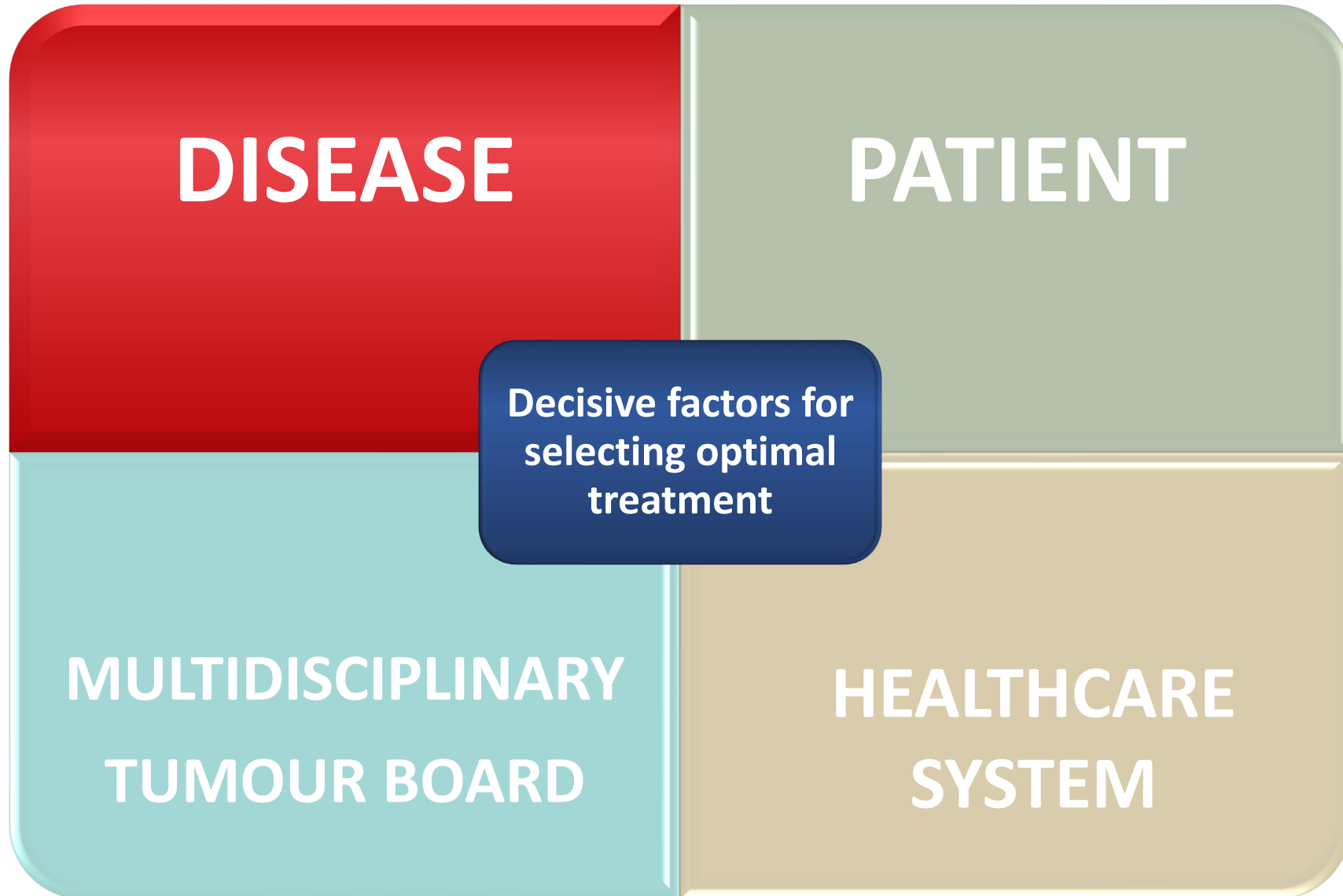
Decisive: showing the ability to make decisions quickly and effectively.
Determines or influences selection.

***Decisive factors for selecting the optimal
treatment of M0 esophageal SCC***

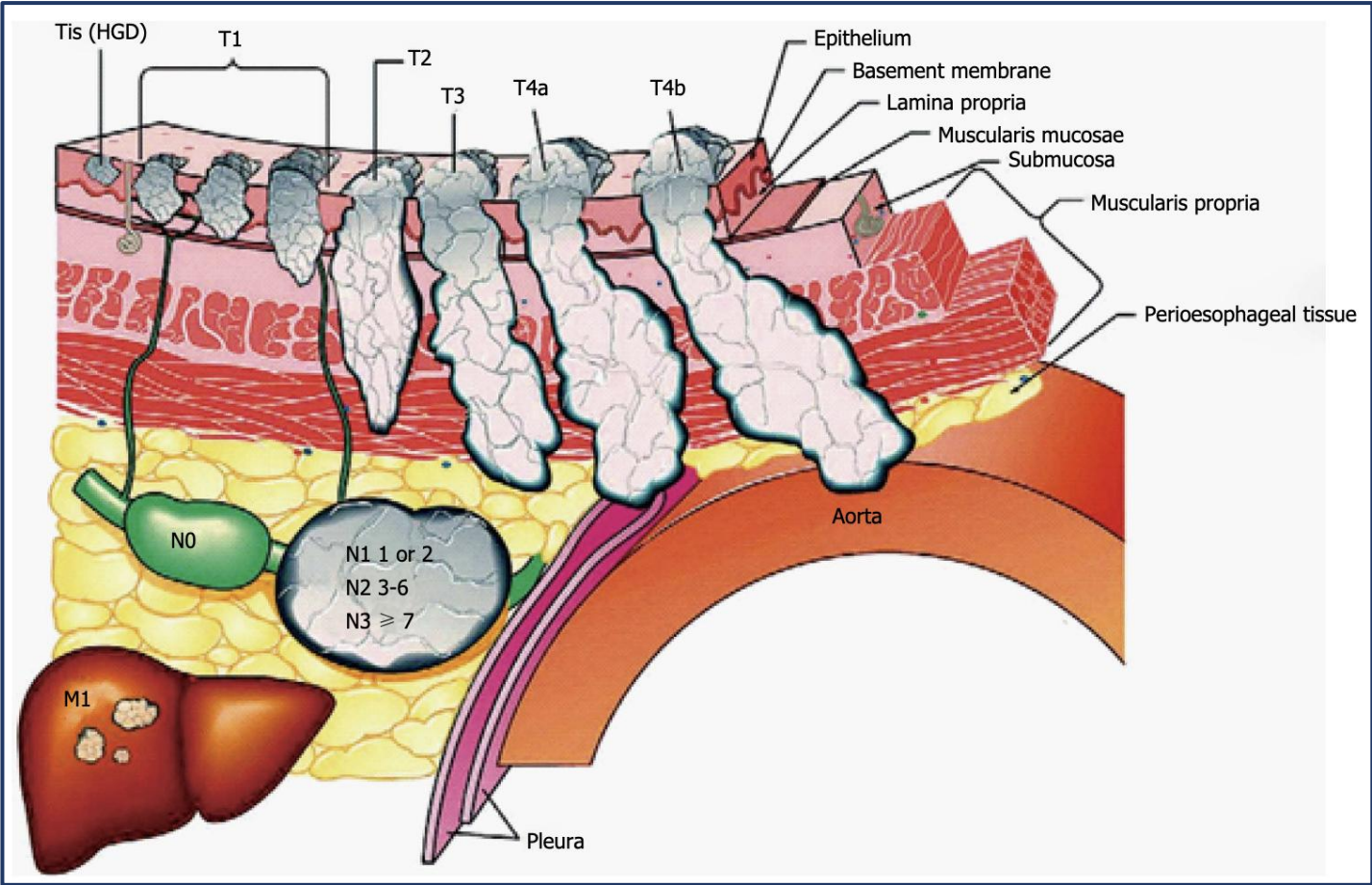
FACTORS



FACTORS

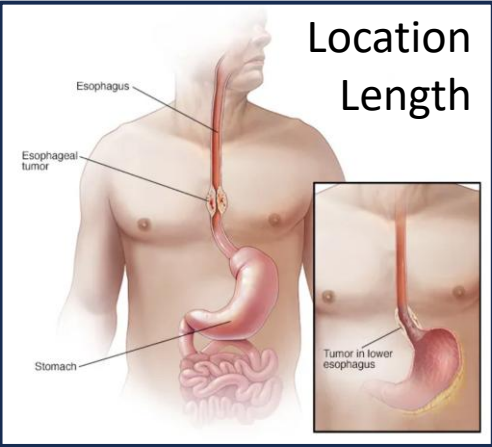


DISEASE: TNM AND LOCATION - LENGTH



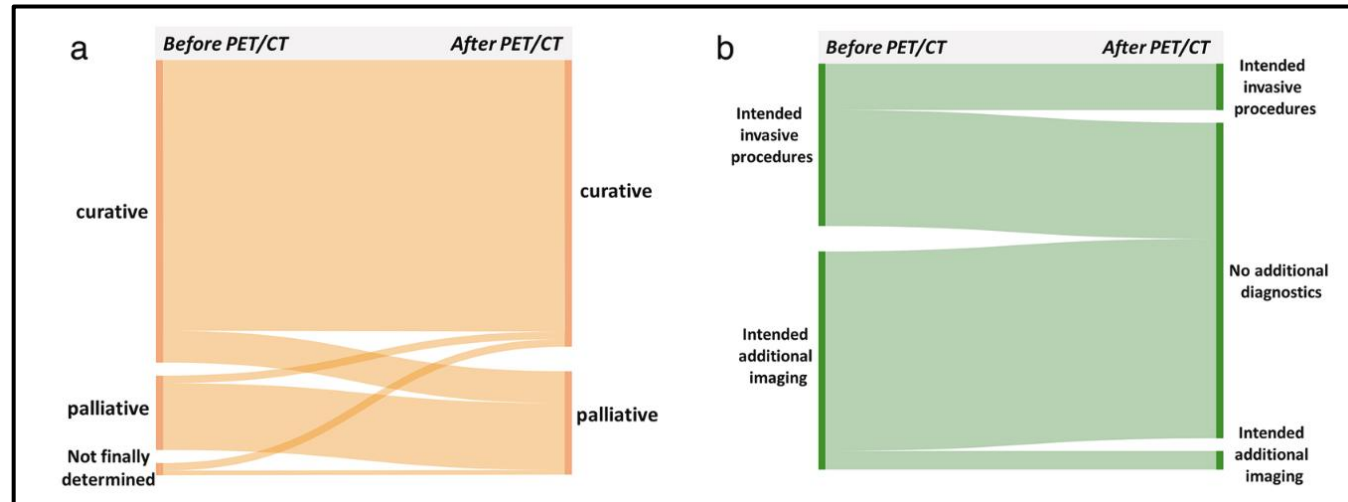
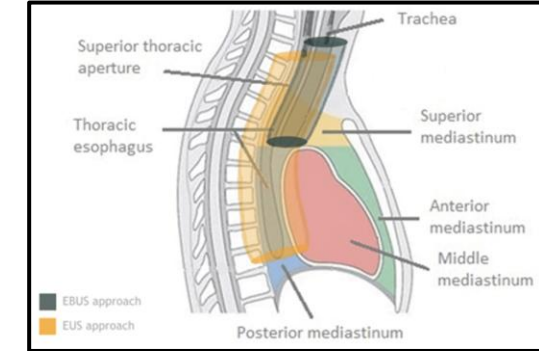
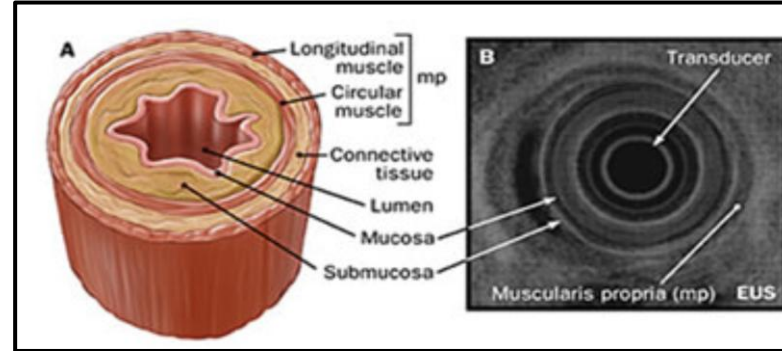
	T1	T2	T3	T4 a	T4 b
N0	I	II	II	IV A	IVA
N1	I	II	III	IV A	IVA
N2	III	III	III	IVA	IVA
N3	IVA	IVA	IVA	IVA	IVA

Stage groupings for M0 esophageal squamous cell carcinoma



DISEASE: STAGING PROCEDURES

Procedure	Purpose
FBC	Assess for iron-deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. PD-L1 and HER2 status (AC)
EUS	Accurate assessment of T and N stage in potentially resectable tumours
Bronchoscopy with endobronchial ultrasonography	Assess tumour growth towards central airways; complementary to EUS, especially when tumour stricture precludes EUS
CT of thorax + abdomen ± pelvis	Staging of tumour to detect local/distant lymphadenopathy and metastatic disease
PET-CT, if available	Staging of tumour to detect local/distant lymphadenopathy and metastatic disease



DISEASE: UNRESECTABLE VS INCURABLE

UNRESECTABLE:

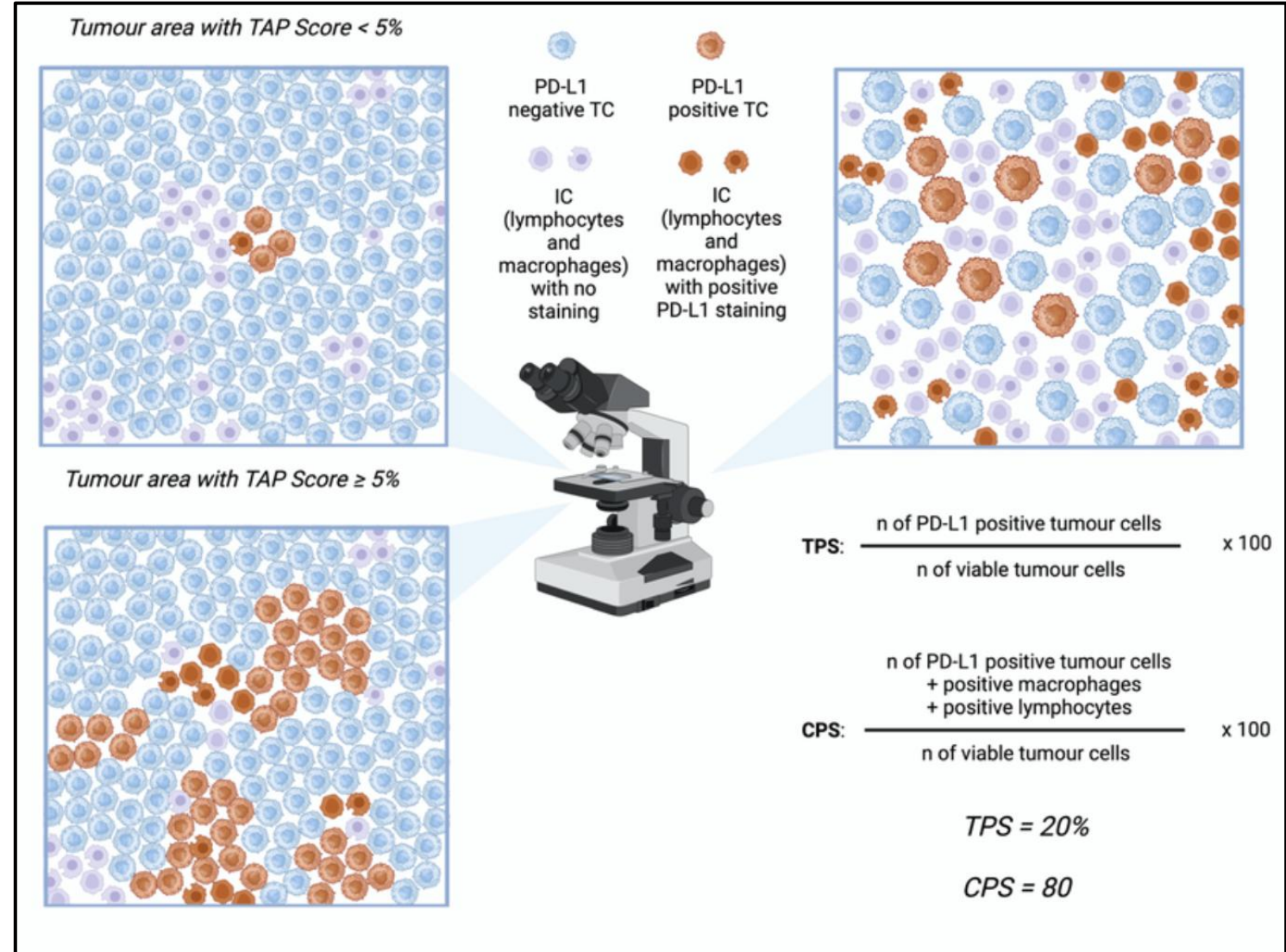
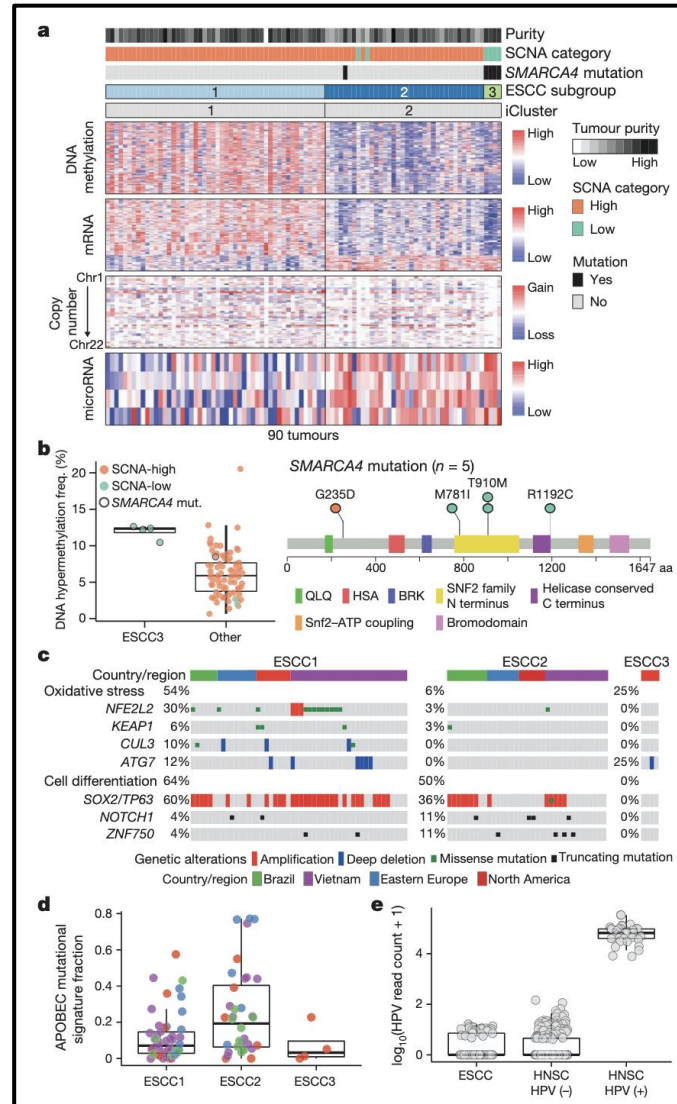
Cancer that can not be completely removed surgically (R0) due to either local tumour invasión into critical adjacent structures or the presence of distante metastatoc disease



NOT AMENABLE TO CURATIVE TREATMENT:

Currently available medical interventions can not reliably achieve the complete and permanente eradication of the disease

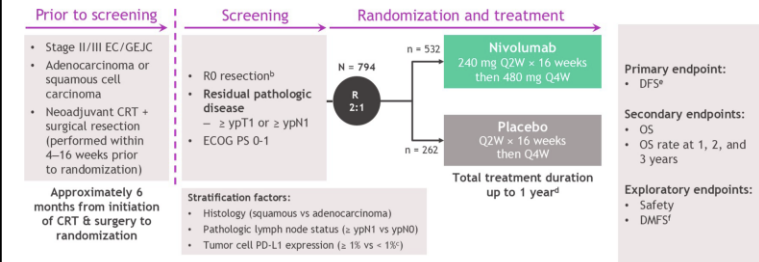
DISEASE: MOLECULAR PATHOLOGY



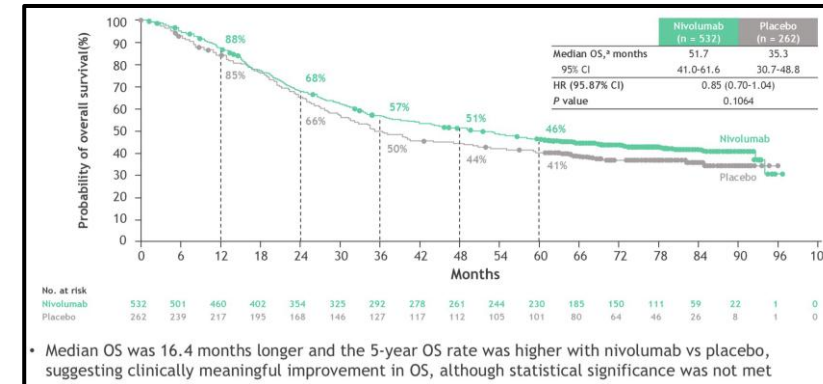
DISEASE: MOL. PATHOLOGY RELEVANCE - LOCALIZED

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial^a



- At the data cutoff (November 7, 2024), the median follow-up was 78.3 months (range, 60.1–96.6)^g



Category	Subgroup	Median OS, mo		Unstratified HR (95% CI)	
		Nivolumab	Placebo		
Overall	N = 794	51.7	35.3	0.85 (0.70-1.03)	
Age, years	< 65 (n = 507)	56.4	36.6	0.83 (0.65-1.06)	
	≥ 65 (n = 287)	39.3	35.2	0.87 (0.64-1.19)	
Sex	Male (n = 671)	45.5	34.7	0.88 (0.72-1.08)	
	Female (n = 123)	NR	48.0	0.70 (0.41-1.19)	
Race ^a	White (n = 648)	49.5	34.8	0.84 (0.68-1.03)	
	Asian (n = 117)	61.5	NR	1.10 (0.63-1.93)	
ECOG PS	0 (n = 464)	60.5	40.3	0.85 (0.66-1.10)	
	1 (n = 330)	37.2	32.1	0.84 (0.63-1.12)	
Disease stage at initial diagnosis ^b	II (n = 278)	58.2	44.1	0.86 (0.62-1.19)	
	III (n = 516)	49.3	32.8	0.84 (0.66-1.06)	
Tumor location at trial entry	Esophagus (n = 467)	49.5	31.4	0.69 (0.54-0.88)	
	Gastroesophageal junction (n = 327)	54.9	64.2	1.14 (0.83-1.56)	
Histologic type ^{c,d}	Adenocarcinoma (n = 563)	51.7	40.2	0.92 (0.73-1.15)	
	Squamous cell carcinoma (n = 230)	50.7	31.4	0.72 (0.51-1.03)	
Tumor cell PD-L1 expression ^e	≥ 1% (n = 120)	60.8	51.2	0.88 (0.51-1.43)	
	< 1% (n = 571)	47.7	34.6	0.82 (0.66-1.02)	
PD-L1 CPS ^f	≥ 1 (n = 585)	45.5	33.5	0.79 (0.64-0.99)	
	< 1 (n = 81)	39.2	52.8	1.40 (0.77-2.56)	
Pathologic lymph node status ^{d,g}	ypN0 (n = 333)	92.8	68.5	0.81 (0.58-1.14)	
	≥ ypN1 (n = 459)	33.6	28.0	0.86 (0.68-1.10)	

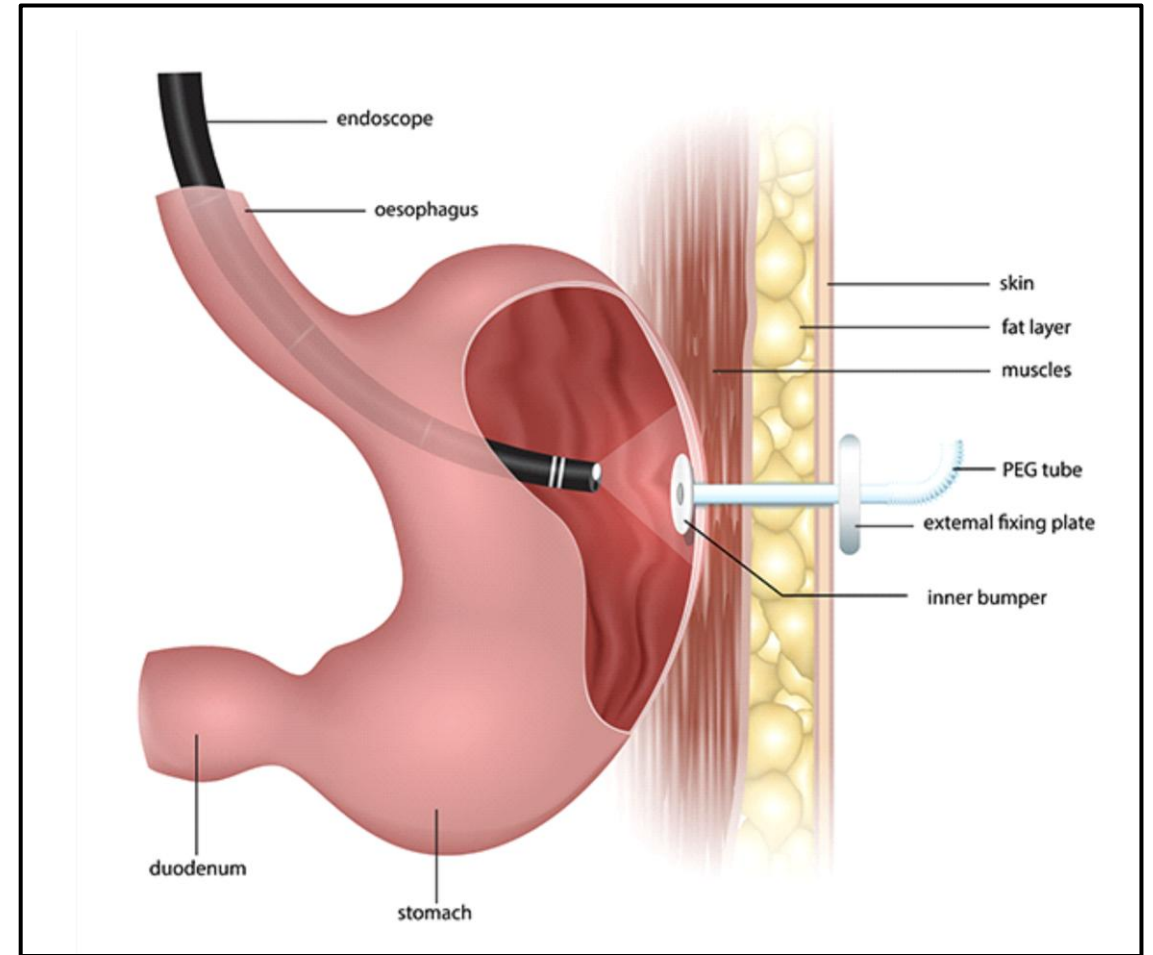
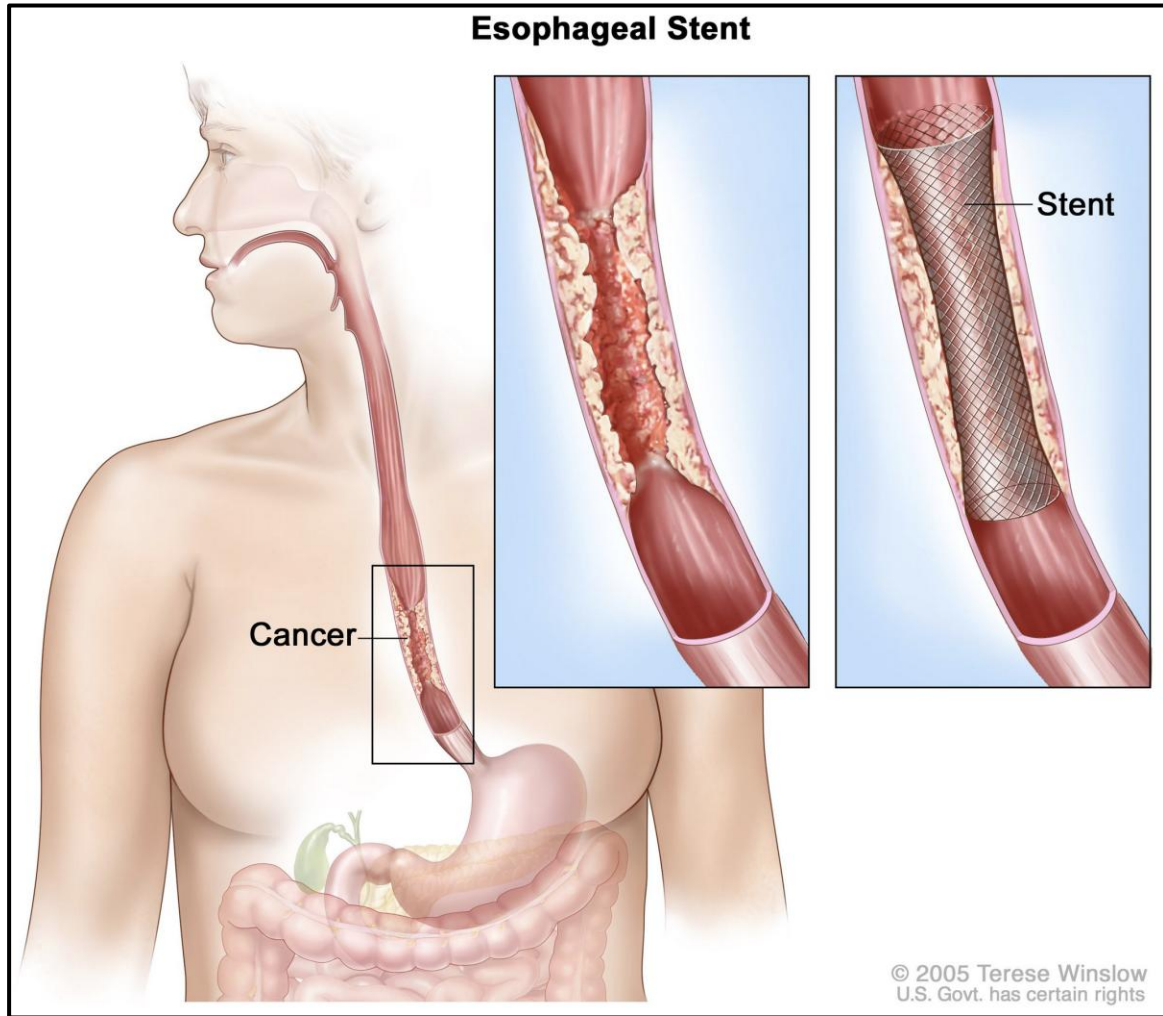
DISEASE: MOL. PATHOLOGY RELEVANCE - ADVANCED

DRUG AND STUDY	DESIGN	BIOMARKER	GLOBAL POPULATION	POPULATION CHARACT.	PRIMARY ENDPOINT	SUBGROUPS	SECONDARY ENDPOINT	TOXICITY	QoL	ESMO MCBS - COST ‡
Pembrolizumab KEYNOTE - 590 <i>Lancet 2021 Oncologist 2024 ASCO GI 2024</i>	Phase III CDDP + FU + Pembrolizumab/ placebo Measurable Dis. Strat.: ECOG, region, histology	PD-L1 CPS ≥ 10 ADC.: 13% SCC: 33% Primary endpoint	LA unresect (9%) or MTS (91%). N: 749 p. ADC (27%) and SCC	ECOG 0-1: 90% Age 63 years. male 84%. Asia 54%.	OS in PD-L1 CPS ≥ 10: HR 0.64 (0.52-0.80)* Δ 4.1 months at 2 y. * FU: 5 y.	OS in SCC and PD-L1 CPS ≥ 10: HR 0.60 (0.46-0.76) Δ 5.1 m.	SCC and PD-L1 CPS ≥ 10 PFS: HR 0.53 (0.41-0.69) Δ ≈ 2 months. RR: 51% vs 28%. DoR: 10.4 vs 4.4 months.	Tox. ≥ G3: 72% vs 68%. Tox. IO: 26% vs 12%. ≥ G3: 7% vs 2% Global population	Similar: - QoL - Time to deterioration Improv. Pain and dysphagia Not ESMO qualified Global population	I, A MCBS 4 v.2.0 – Form 2A SNS financed €€€
Nivolumab CHECKMATE - 648 <i>N Eng J Med 2022 ASCO 2022 ESMO GI 2024 ESMO Gastr Oncol 2025</i>	Phase III CDDP + FU +/- Nivolumab * Measurable Dis. Strat.: ECOG, region, PD-L1 TPS, MTS	PD-L1 TPS ≥ 1% SCC.: 49% Primary endpoint	LA unresect. (15%) or MTS (80%). N: 645 p. SCC 100%.	ECOG 0-1: 100% Age 64 years. Males 82%. Asia 71%. MTS ≥ 2: 51%	OS in PD-L1 TPS ≥ 1%: HR 0.60 (0.47-0.77) Δ 5.9 months. FU: 4 y.		PD-L1 TPS ≥ 1% PFS: HR 0.67 (0.51-0.88) Δ 2.4 months. RR: 53% vs 20%. DoR: 8.4 vs 5.7 onths	Tox. ≥ G3: 47% vs 36%. Tox. IO: 90% vs 44%. ≥ G3: 9% vs 5% Global population	Similar: - QoL Improvement Q-TWiST (Post hoc) Not ESMO qualified Global population	I, A MCBS 4 v.2.0 – Form 2A SNS financed €€
Tislelizumab RATIONALE - 306 <i>Lancet 2023 Oncologist 2024 ASCO GI 2024 ISPOR 2024</i>	Phase III Cis/oxa + FP/ pacl+ tislelizum. /placebo Measurable, evaluable Dis. Strat.: QMT, region, previous treatment	PD-L1 TAP ≥ 5% Epiderm.: 55% NO Primary endpoint	LA unresect (14%) or MTS (86%). N: 649 p. SCC 100%.	ECOG 0-1: 100% Age 64 years. Male 87%. Asia 75%. MTS ≥ 2: 17%	OS in PD-L1 TAP ≥ 5%: HR 0.61 (0.48-0.78) Δ 9.1 months. FU: 3.5 y.	LA unresectable TAP ≥ 5%. N: 45p. OS: HR 0.37 (0.16-0.83) PFS: HR 0.44 (0.19-1.02)	PD-L1 TAP ≥ 5% SLP: HR 0.50 (0.39-0.65) Δ 2.7 months. RR: 71% vs 41%. DoR: 7.1 vs 5.4 months.	Tox. ≥ G3: 70.2% vs 66.5%. Tox. IO: 42.7% vs 21.6%. ≥ G3: 8.8% vs 2.2% Pop. TAP ≥ 5	Trend to improvement in pain and less worsening of functional status Not ESMO qualified Global population	I, A MCBS 4 v.2.0 – Form 2A SNS financed €

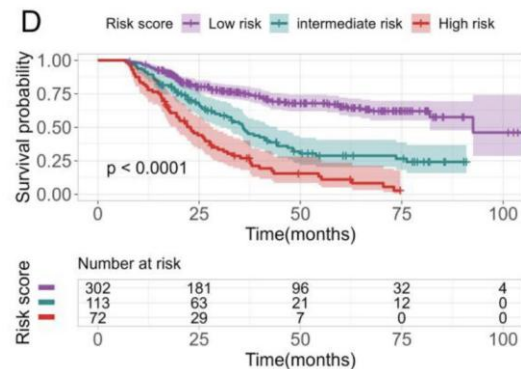
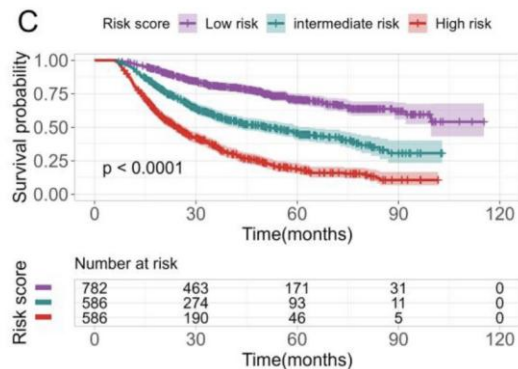
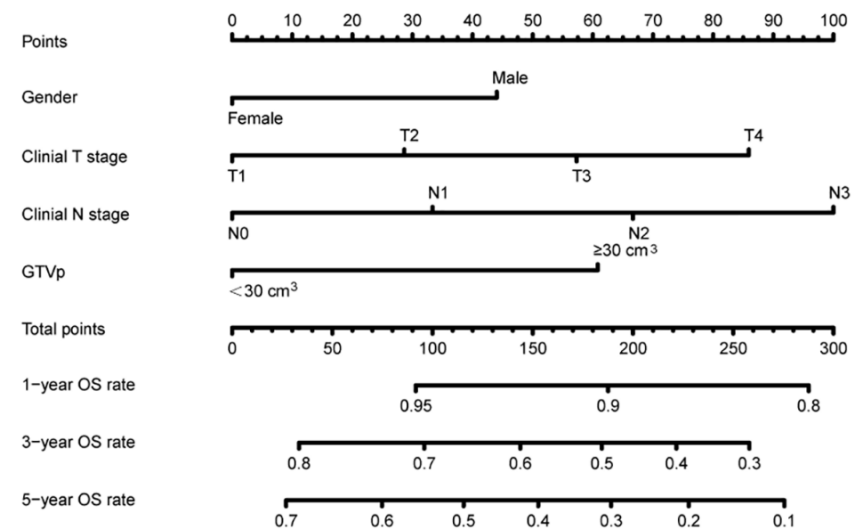
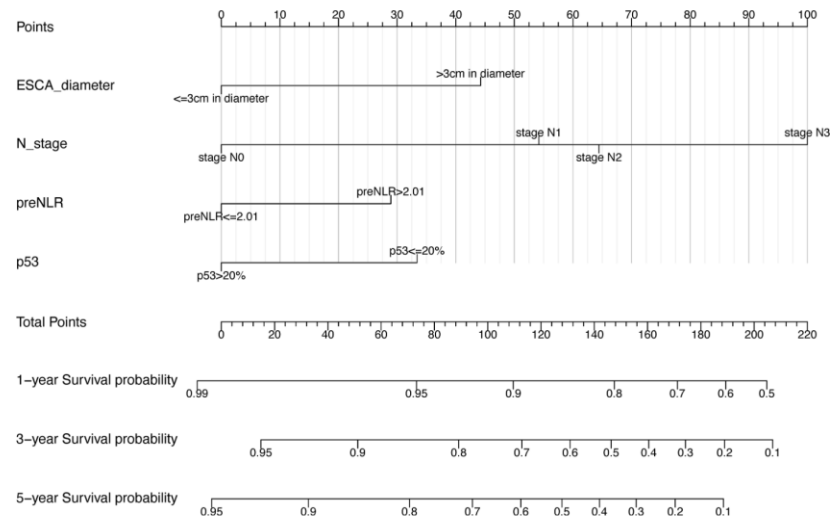
*Nivolumab-Ipilimumab non-SNS financed.

‡ Simplified QUALY cost (Hospitalaria del HGU Elche).

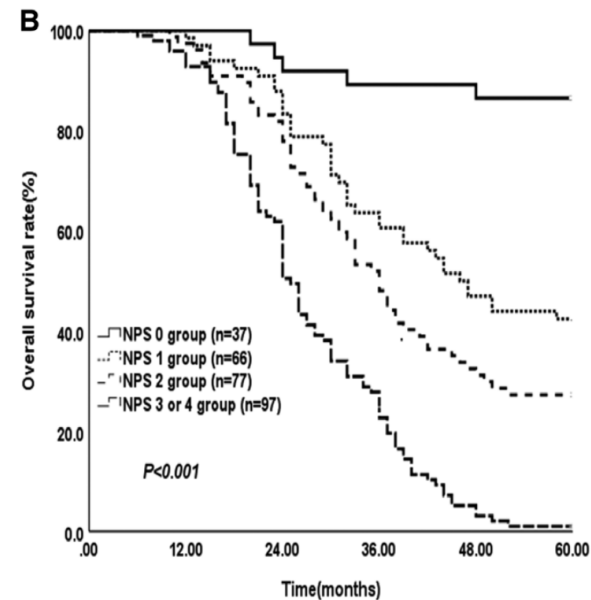
DISEASE: SYMPTOMS



DISEASE: IMPACT - PROGNOSIS



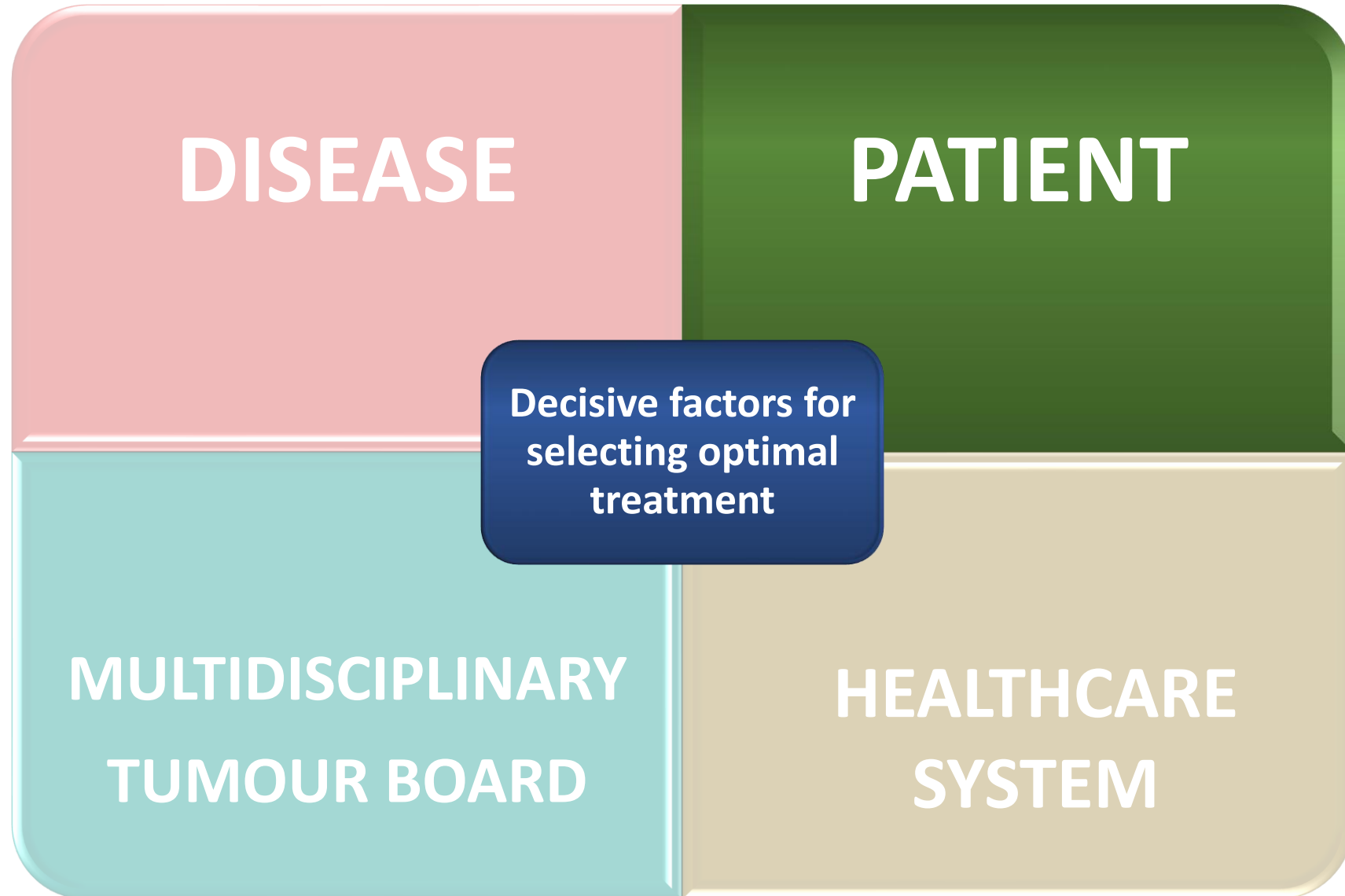
Risk groups	Training cohort		Validation cohort	
	3-year survival	5-year survival	3-year survival	5-year survival
Low risk	80.8% (77.9–84.0)	70.6% (66.5–74.9)	75.4% (70.3–80.9)	65.3% (59.0–72.2)
Intermediate risk	58.2% (53.9–62.7)	45.6% (40.8–51.0)	48.8% (39.6–60.1)	29.7% (20.3–40.6)
High risk	29.5% (25.8–33.7)	18.7% (15.1–23.0)	26.9% (18.1–40.1)	11.0% (5.1–23.6)



Calculation of Naples prognostic score (NPS).				
Variables	PFS		OS	
	Cutoff value	Points	Cutoff value	Points
Alb (g/L)	≥ 41.1	0	≥ 41.2	0
	< 41.1	1	< 41.2	1
TC (mg/dL)	> 205.7	0	> 202.2	0
	≤ 205.7	1	≤ 202.2	1
NLR	≤ 2.7	0	≤ 2.8	0
	> 2.7	1	> 2.8	1
LMR	> 3.3	0	> 3.1	0
	≤ 3.3	1	≤ 3.1	1

Alb = albumin, LMR = lymphocyte to monocyte ratio, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PFS = progression-free survival, TC = total cholesterol.

FACTORS



PATIENT: PREFERENCES – PERSPECTIVES - ATTITUDE

ASCO Guideline:

- Treatment decisions should be made through **shared decision-making**, incorporating not only clinical factors but also patient values, preferences, and support systems.
- This includes a **thorough discussion of the risks, benefits**, and potential outcomes of each option, and recognizes that **patient preference** is a key determinant in the decision to pursue surgery, chemoradiotherapy, or other modalities

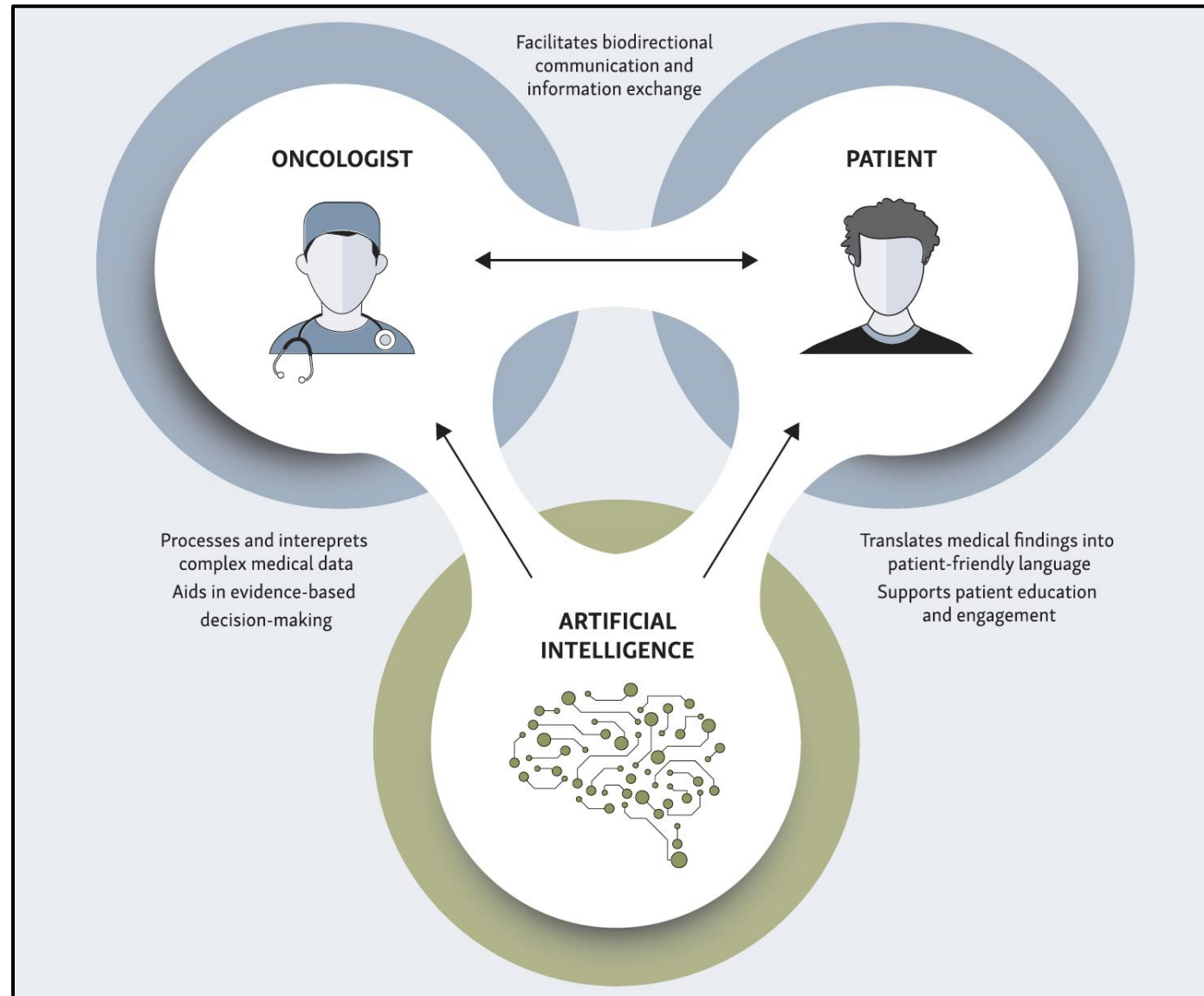
The NOSANO - study:

- Patients' coping styles, **attitudes toward uncertainty**, and **desire for organ preservation or quality of life** are major factors in treatment selection.
- These preferences are not solely determined by medical contraindications or comorbidities.

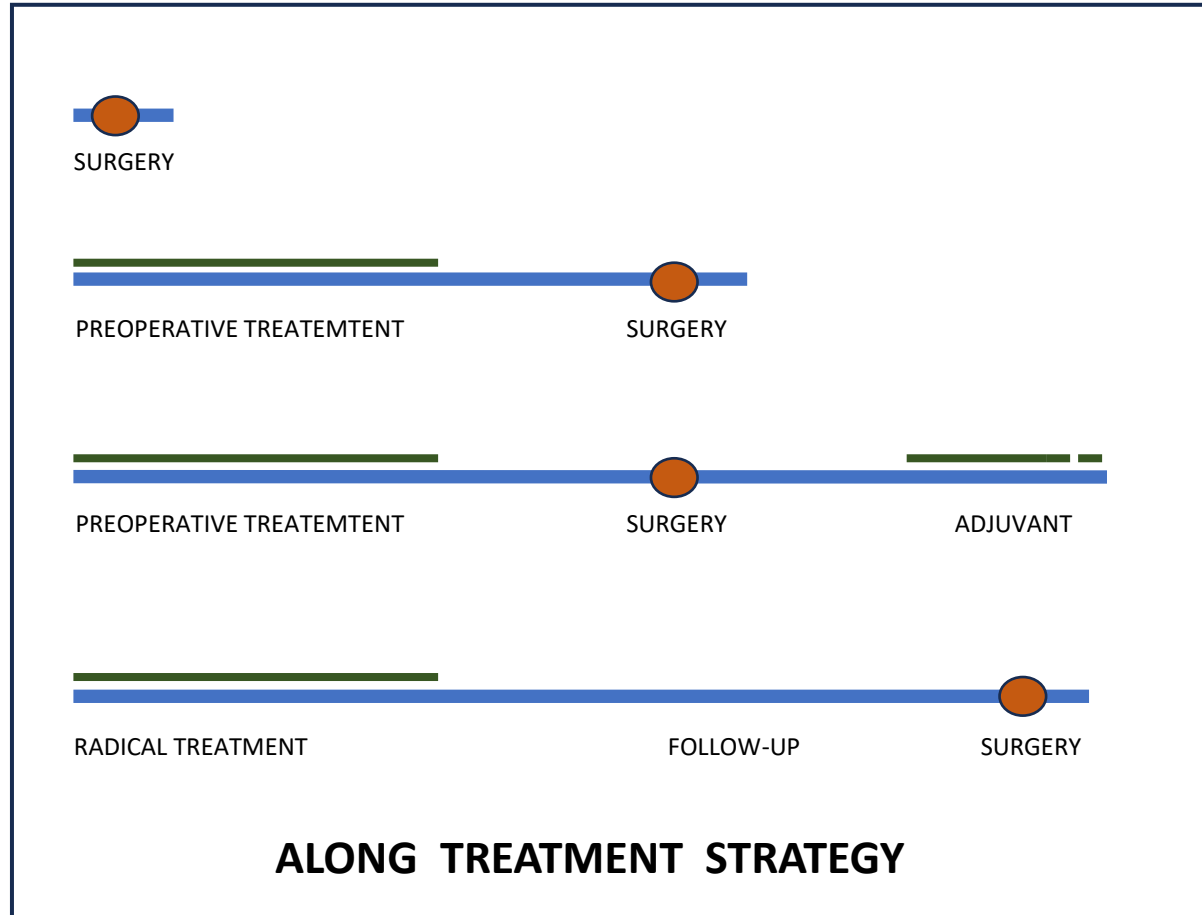
The JCOG0502 - study:

- Factors such as age, family structure, and the influence of **physician recommendations** also play a role in patient decision-making, with the physician's opinion often being the most influential non-medical factor

PATIENT: PREFERENCES – PERSPECTIVES - ATTITUDE



PATIENT: MEDICAL CONDITION - APTITUDE



Functional status

Comorbidities

Polypharmacy

CGA

Nutritional status

Disease – related symptoms

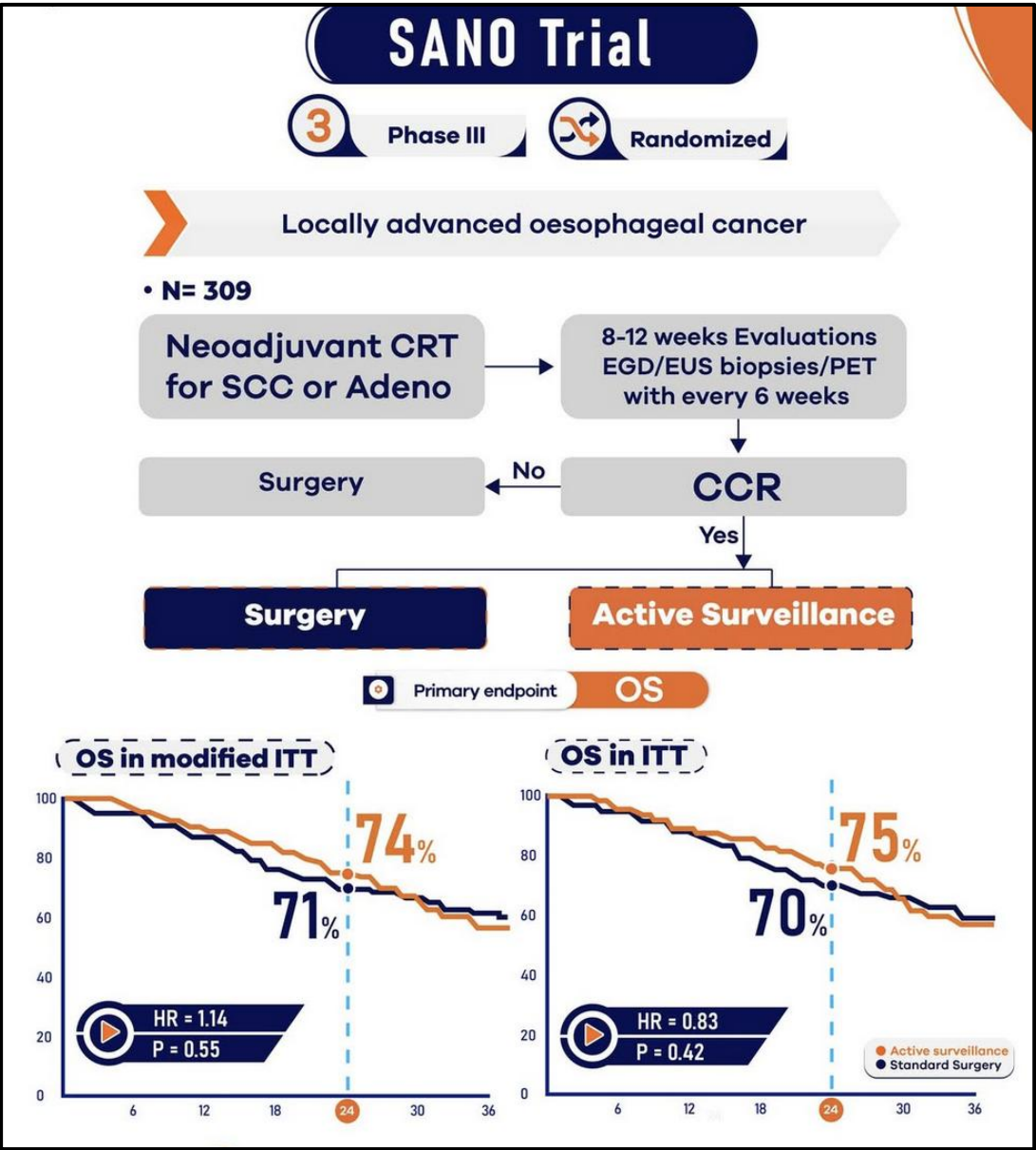
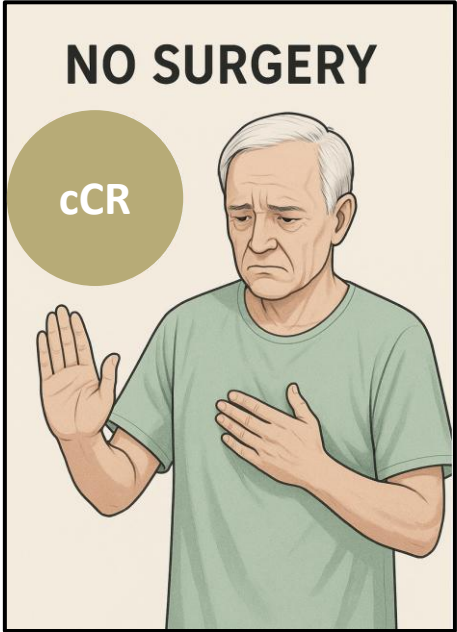
Operability

Previous treatments

Treatment adherence

Toxicity - Complications

PATIENT: DYNAMIC CONDITION – PREFERENCES



	Active surveillance (n=83)	Standard surgery (n=101)
Any complication	68 (82%)	85 (84%)
Anastomotic leakage	18 (22%)	27 (27%)
Severity of anastomotic leakage		
Subclinical, spontaneous recovery	2 (2%)	3 (3%)
Subclinical, requiring surgery	1 (1%)	0
Clinical, spontaneous recovery	10 (12%)	15 (15%)
Clinical, requiring surgery	5 (6%)	9 (9%)
Pulmonary complications		
Any	39 (47%)	64 (63%)
Pneumonia	20 (24%)	29 (29%)
Respiratory failure requiring reintubation	2 (2%)	5 (5%)
Cardiac complications		
Any	28 (34%)	44 (44%)
Dysrhythmia requiring intervention	11 (13%)	20 (20%)
Vocal cord outcome		
Normal vocal cord	71 (86%)	94 (93%)
Vocal cord dysfunction, unilateral	3 (4%)	3 (3%)
Vocal cord dysfunction, bilateral	2 (2%)	1 (1%)
Unknown vocal cord dysfunction	7 (8%)	3 (3%)
Thromboembolic complications		
Pulmonary embolus	0	2 (2%)
Adverse events from clinical response evaluations		
PET-CT	0	0
Endosonography with fine-needle aspiration	1 (1%)	0
Endoscopy with biopsies	0	0
Chylothorax, requiring TPN	3 (4%)	10 (10%)
Chylothorax, requiring surgery	0	1 (1%)
Multi-organ failure	1 (1%)	1 (1%)
Length of ICU stay, days	2 (1-2)	2 (1-3)
Length of hospital stay, days	10 (8-17)	11 (8-17)
30-day mortality	1 (1%)	3 (3%)
90-day mortality	3 (4%)	5 (5%)

Data are n (%) or median (IQR). Percentages represent the occurrence of complications, as part of the total. TPN=total parenteral nutrition. ICU=intensive care unit.

Table 2: Postoperative complications and serious adverse events from clinical response evaluations of patients undergoing oesophagectomy



PATIENT: DYNAMIC CONDITION – PREFERENCES (II)

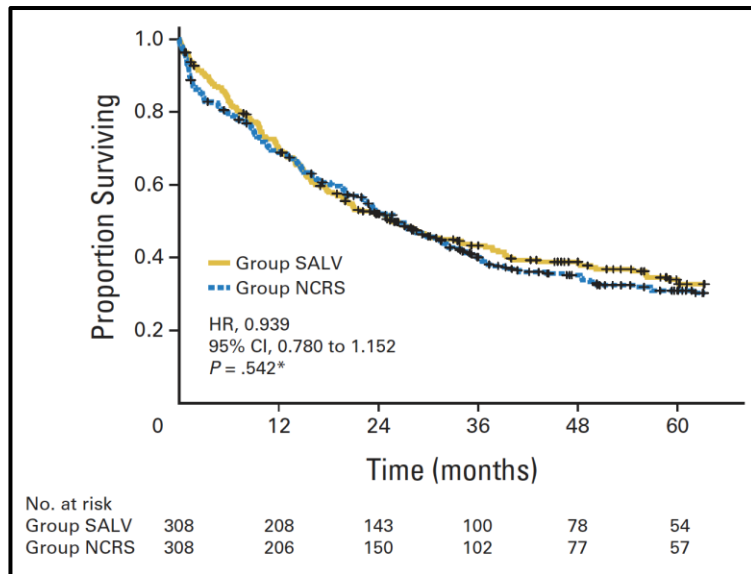


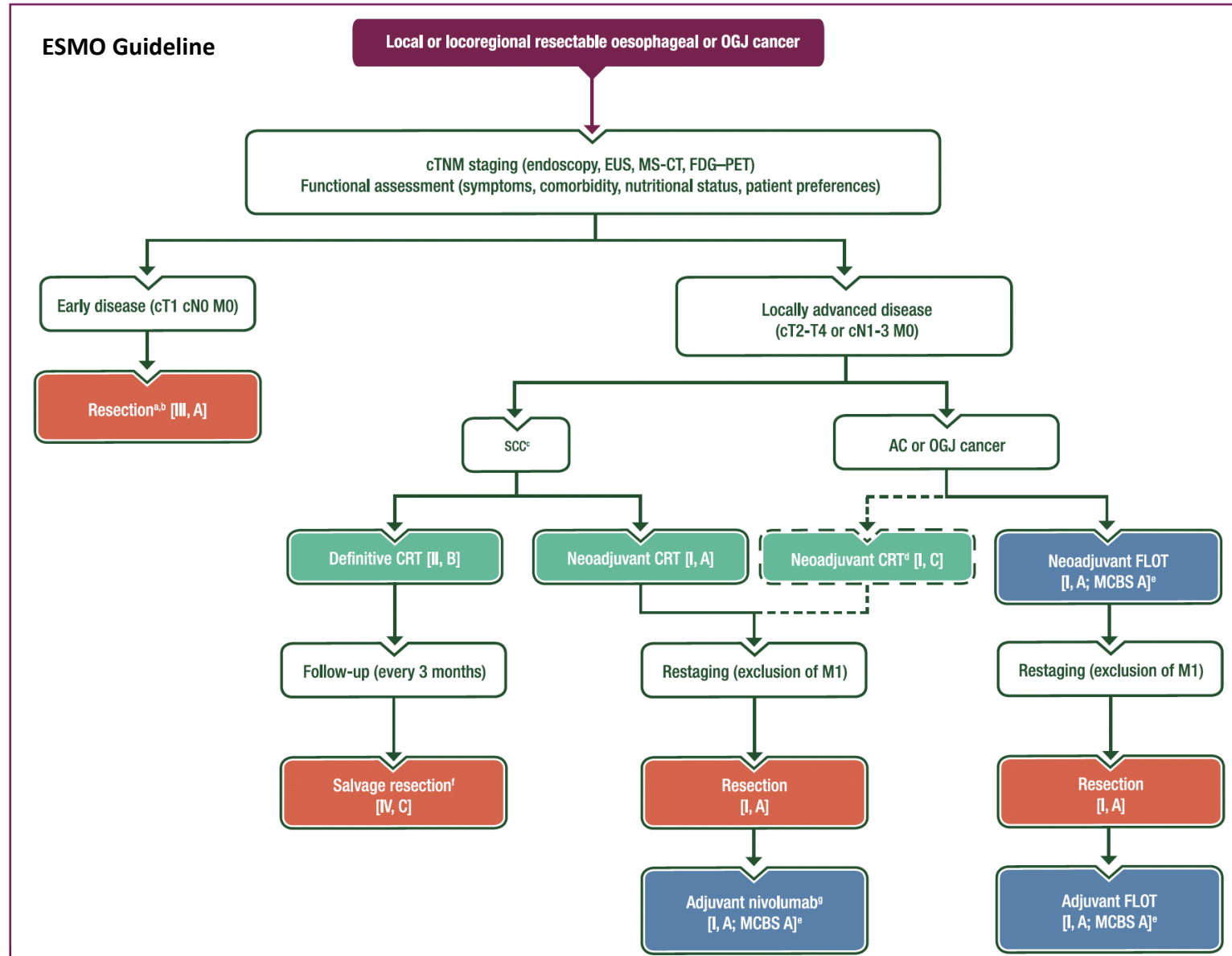
Table 2. Comparison of In-Hospital Mortality and Morbidity in SALV and NCRS Groups

Variable	Overall (N = 848)	Before Matching				After Matching			
		SALV (n = 308)	NCRS (n = 540)	OR (95% CI)	P	SALV (n = 308)	NCRS (n = 308)	OR (95% CI)	P
Outcome									
In-hospital mortality, No. (%)	76 (9.0)	26 (8.4)	50 (9.3)	0.904 (0.550 to 1.484)	.688	26 (8.4)	35 (11.4)	0.719 (0.414 to 1.250)	.241
In-hospital morbidity, No. (%)	514 (60.6)	196 (63.6)	318 (58.9)	1.222 (0.915 to 1.630)	.174	196 (63.6)	188 (61.0)	1.117 (0.818 to 1.525)	.506
Complications									
Anastomotic leak, No. (%)	111 (13.1)	53 (17.2)	58 (10.7)	1.727 (1.155 to 2.582)	.007	53 (17.2)	33 (10.7)	1.732 (1.110 to 2.703)	.015
Conduit necrosis, No. (%)	6 (0.7)	4 (1.3)	2 (0.4)	—	NA*	4 (1.3)	1 (0.3)	—	NA*
Surgical site infection, No. (%)	123 (14.5)	57 (18.5)	66 (12.2)	1.631 (1.109 to 2.399)	.012	57 (18.5)	38 (12.3)	1.614 (1.058 to 2.461)	.026
Chylothorax, No. (%)	26 (3.1)	10 (3.2)	16 (3.0)	1.099 (0.492 to 2.453)	.818	10 (3.3)	10 (3.3)	1.000 (0.404 to 2.474)	> .999
Postoperative hemorrhage, No. (%)	5 (0.6)	1 (0.3)	4 (0.7)	—	NA*	1 (0.3)	3 (1.0)	—	NA*
Gastroparesis, No. (%)	10 (1.2)	6 (1.9)	4 (0.7)	—	NA*	3 (1.0)	3 (1.0)	—	NA*
Pulmonary, No. (%)	353 (41.6)	132 (42.9)	221 (40.9)	1.083 (0.815 to 1.437)	.583	132 (42.9)	127 (41.2)	1.069 (0.786 to 1.454)	.672
Cardiovascular, No. (%)	115 (13.6)	42 (13.6)	73 (13.5)	1.010 (0.671 to 1.521)	.962	42 (13.6)	43 (14.0)	0.973 (0.612 to 1.547)	.908
Thromboembolic, No. (%)	25 (2.9)	9 (2.9)	16 (3.0)	0.989 (0.443 to 2.324)	.973	9 (2.9)	10 (3.3)	0.900 (0.374 to 2.167)	.814
Neurologic, No. (%)	25 (2.9)	6 (1.9)	19 (3.5)	1.010 (0.687 to 1.235)	.388	5 (1.6)	8 (2.6)	0.998 (0.876 to 1.113)	.405
Clavien-Dindo score, No. (%)				—	.461			—	.201
I	64 (7.5)	21 (6.8)	43 (8.0)			21 (6.8)	30 (9.7)		
II	168 (19.8)	68 (22.1)	100 (18.5)			68 (22.1)	45 (14.6)		
IIIa	51 (6)	20 (6.5)	31 (5.7)			20 (6.5)	21 (6.8)		
IIIb	49 (5.8)	23 (7.5)	26 (4.8)			23 (7.5)	18 (5.8)		
IVa	86 (10.1)	33 (10.7)	53 (9.8)			33 (10.7)	30 (9.7)		
IVb	20 (2.4)	5 (1.6)	15 (2.8)			5 (1.6)	9 (2.9)		
V	76 (9)	26 (8.4)	50 (9.3)			26 (8.4)	35 (11.4)		

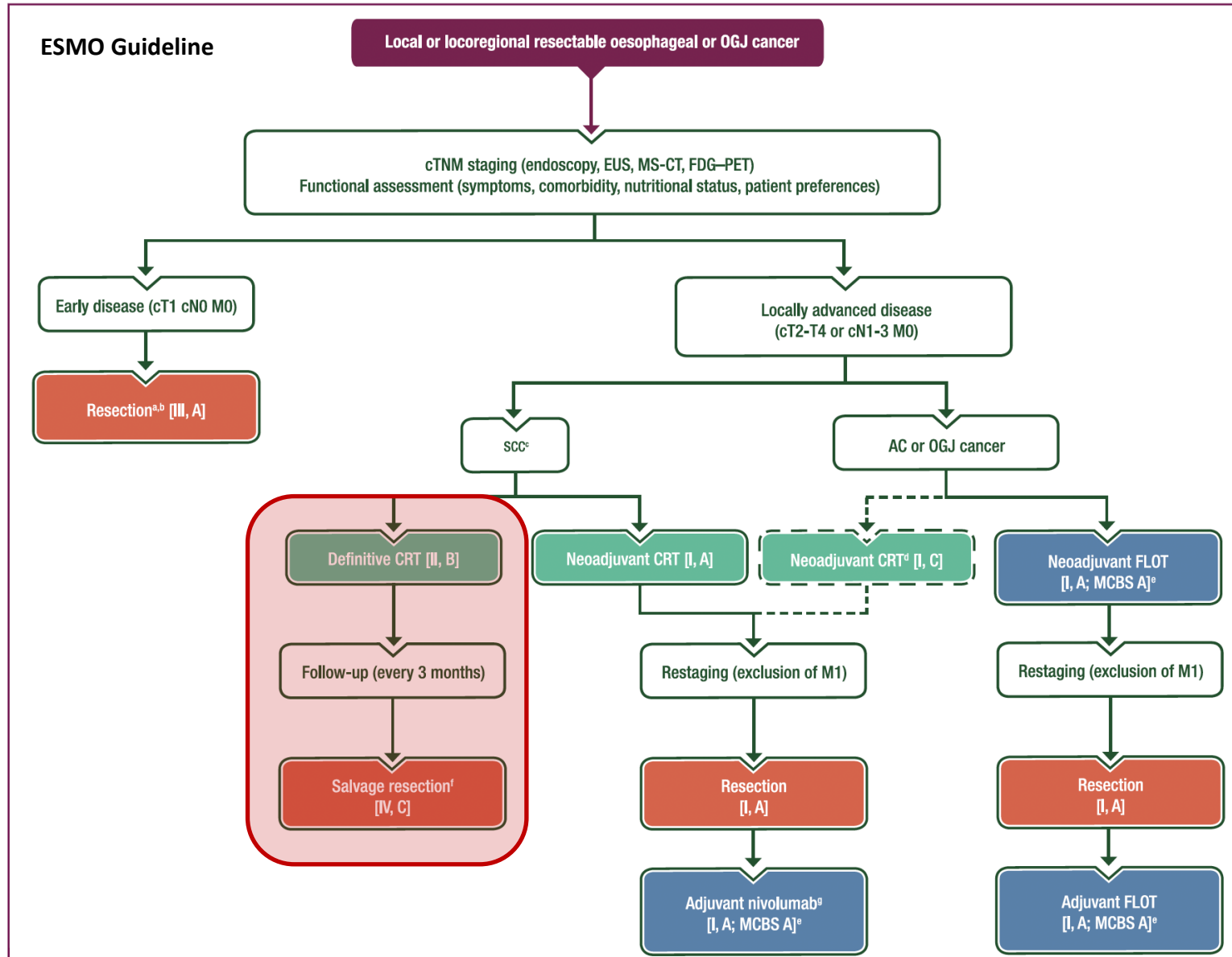
Abbreviations: NA, not applicable; NCRS, neoadjuvant chemoradiotherapy followed by planned esophagectomy; OR, odds ratio; SALV, salvage esophagectomy after definitive chemoradiotherapy.

*Because of low number of events.

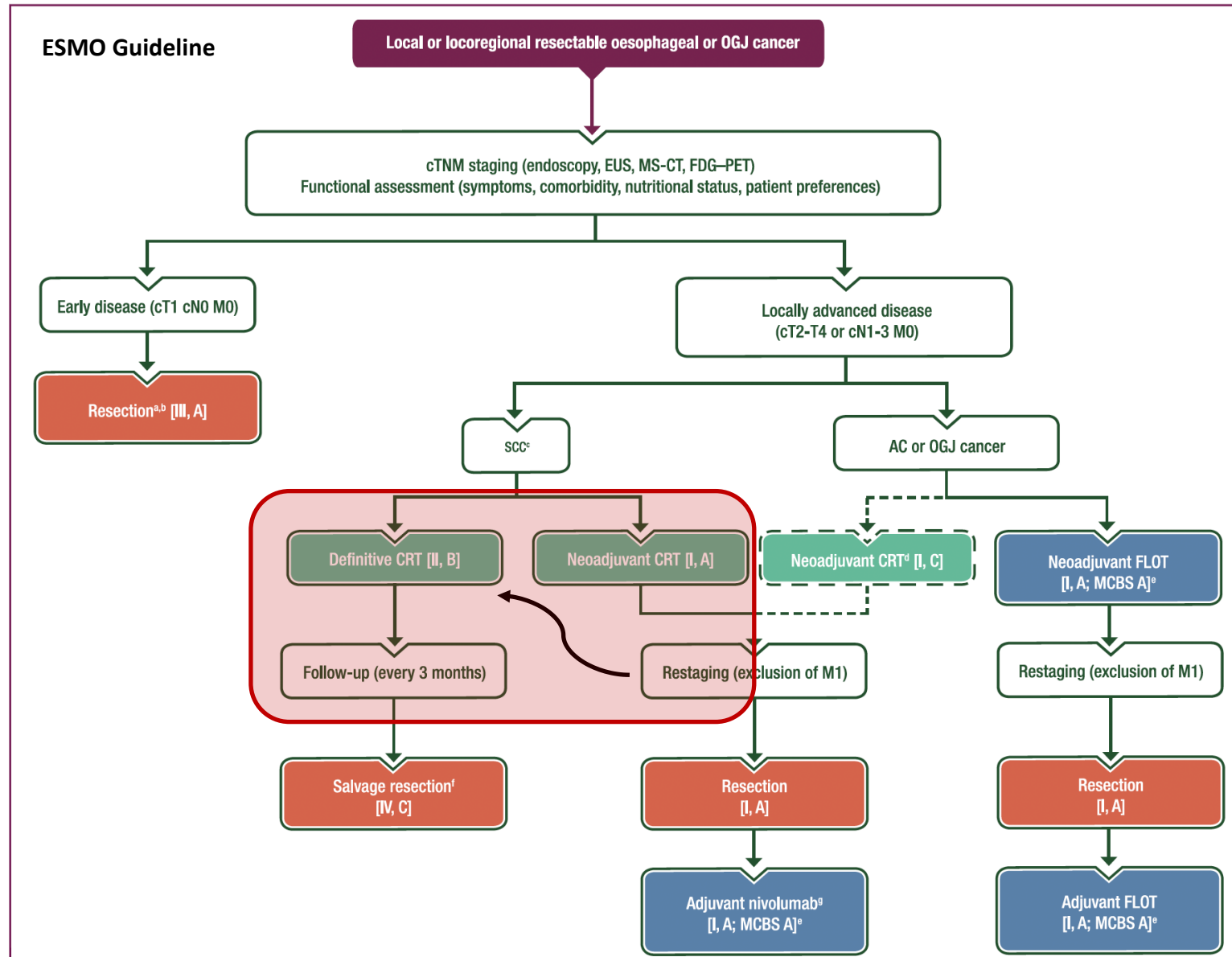
DISEASE AND PATIENT: FIXED PATH



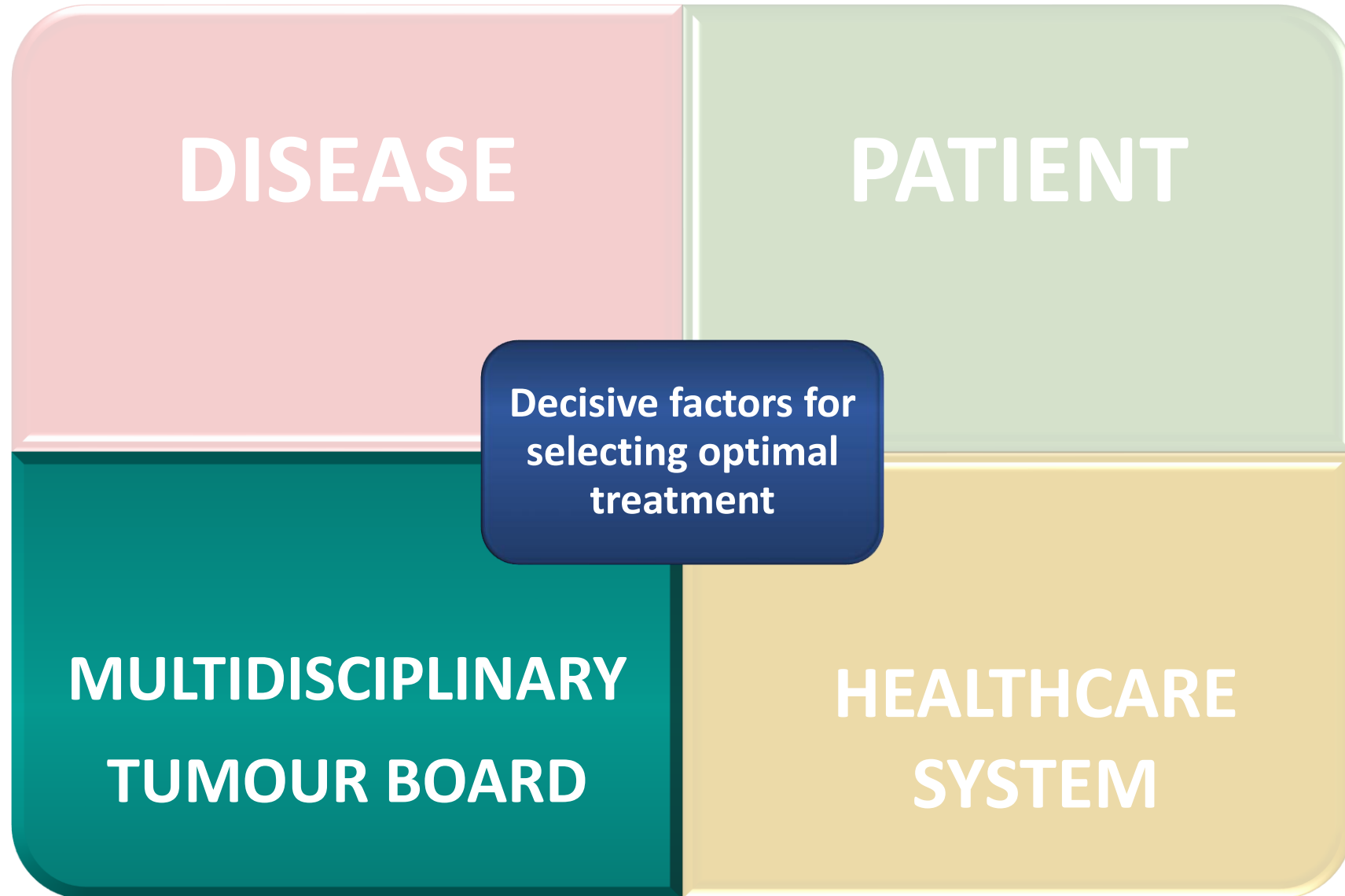
DISEASE AND PATIENT: DYNAMIC PATH



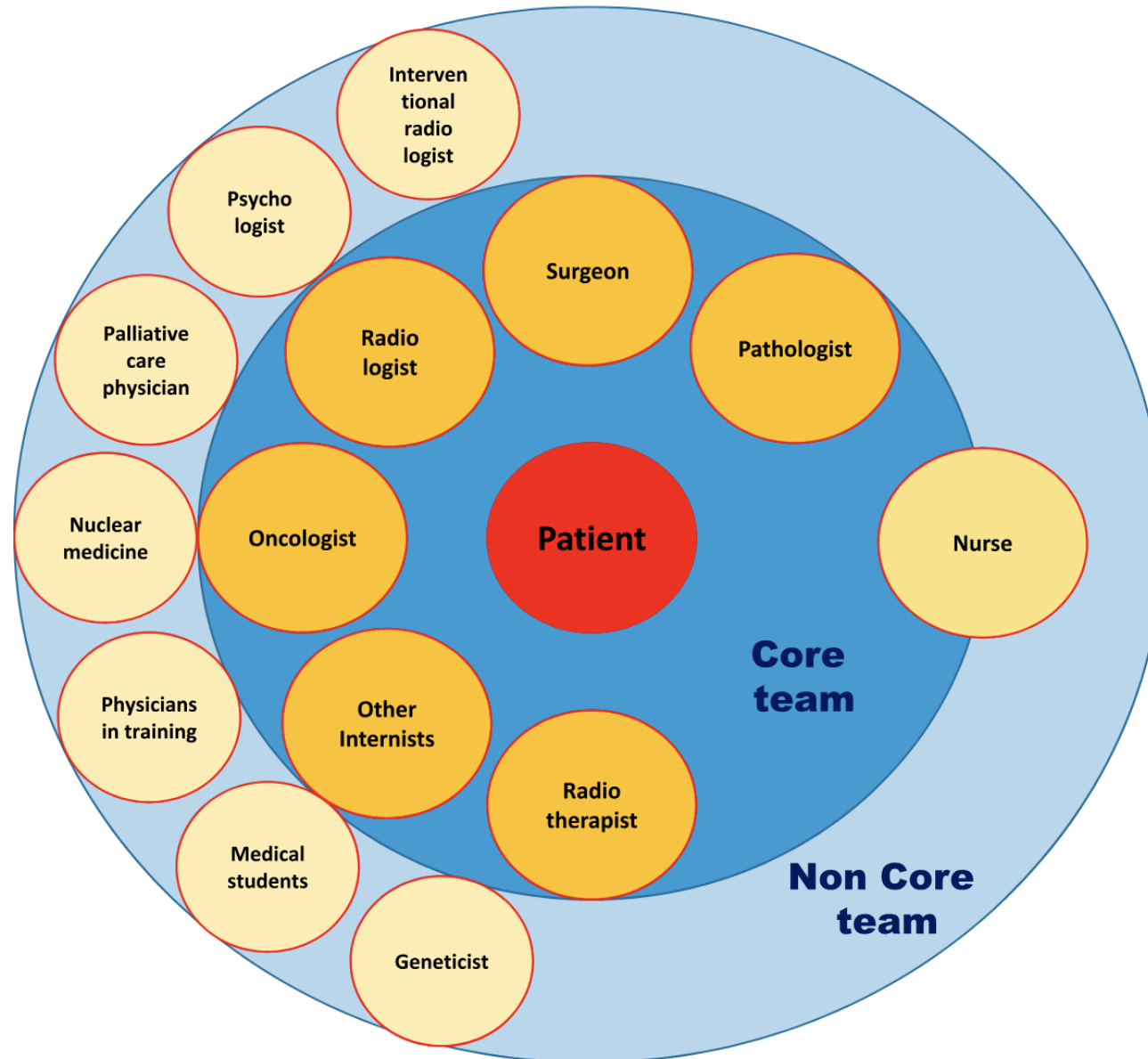
DISEASE AND PATIENT: DYNAMIC PATH



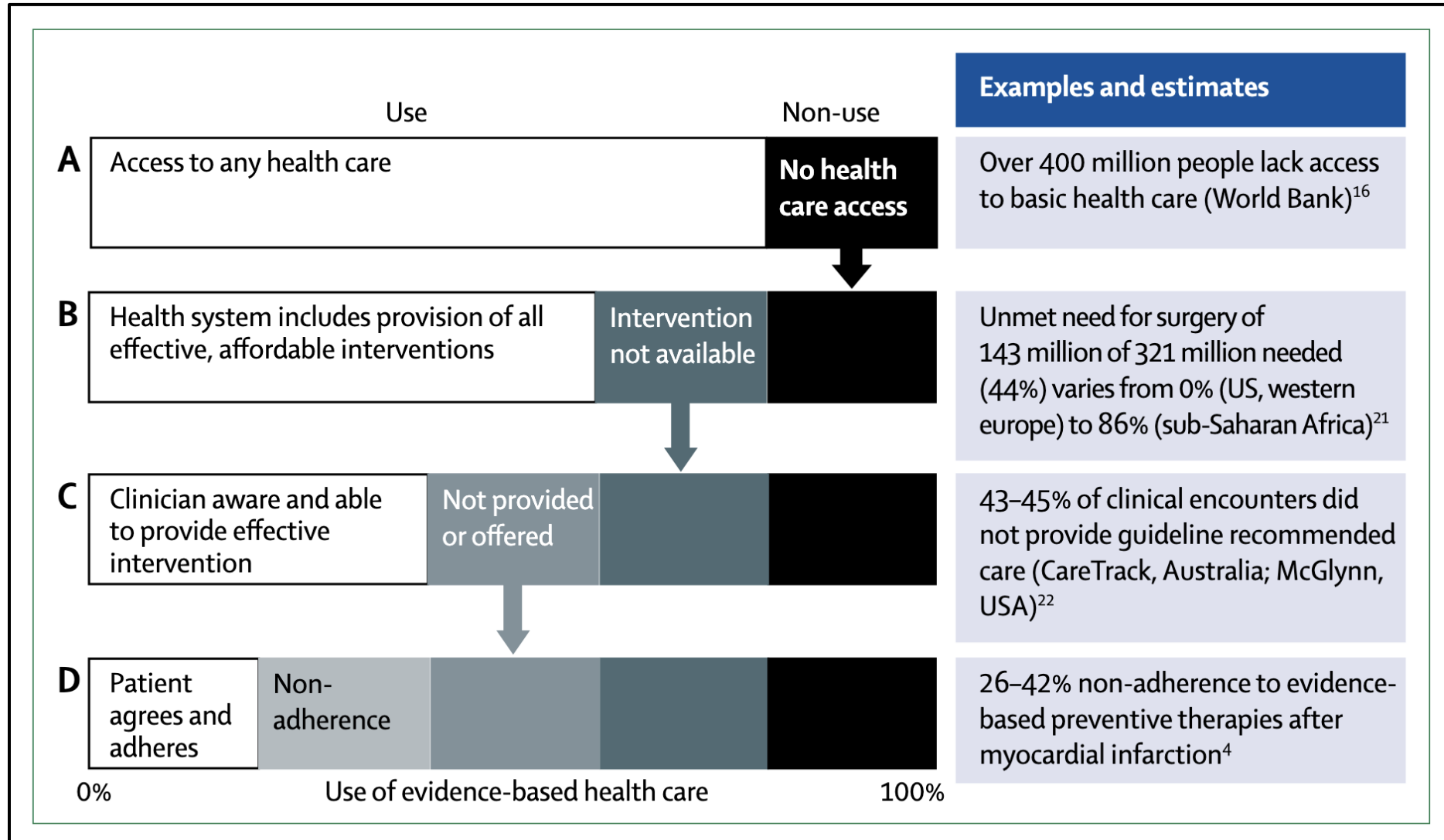
FACTORS



MTB: MULTIDISCIPLINARY APPROACH



MTB: FROM ACCESS TO ADHERENCE



Stages of care, from access to adherence, and underuse risks

American Society for Gastrointestinal Endoscopy Guideline

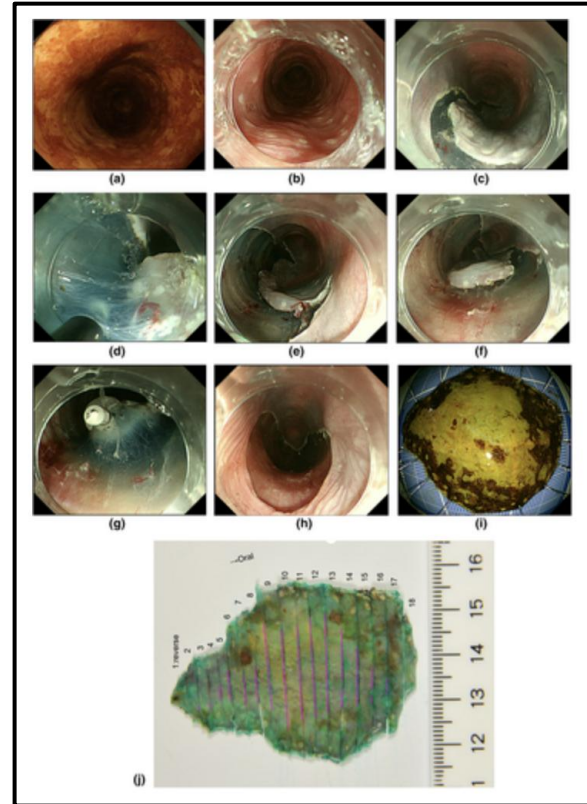
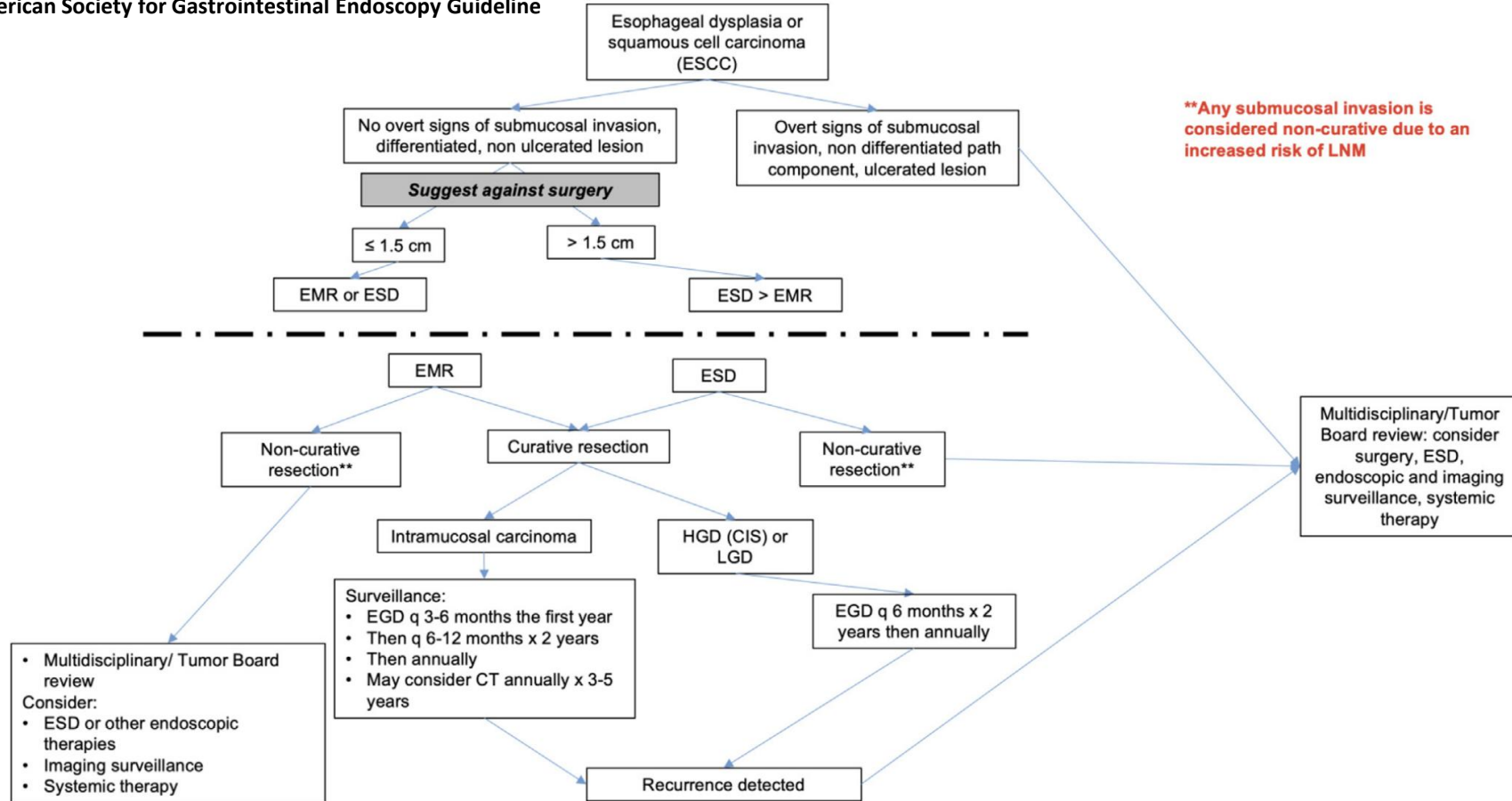
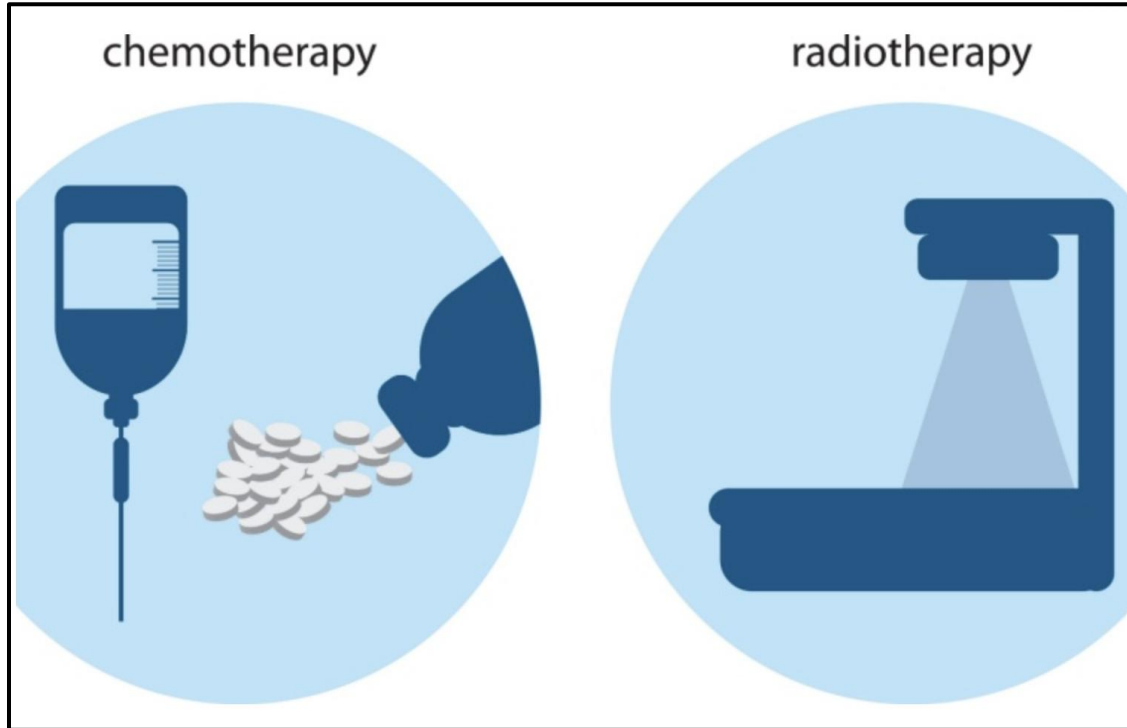
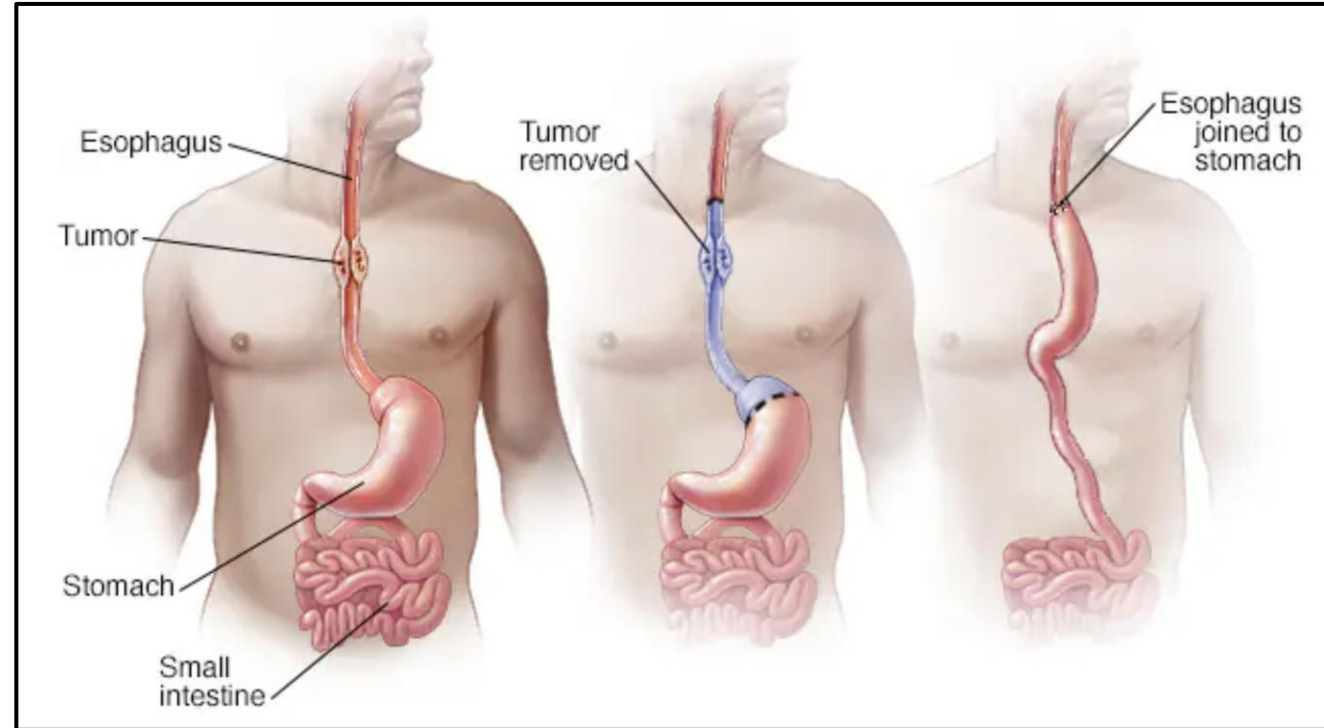


Figure 1. Recommended clinical care algorithm for patients presenting with early-stage ESCC. *ESCC*, Esophageal squamous cell carcinoma; *ESD*, endoscopic submucosal dissection; *LNM*, lymph node metastasis; *HGD*, high-grade dysplasia; *CIS*, carcinoma in situ; *LGD*, low-grade dysplasia.

MTB: PREFERRED OPTIONS - HABITS

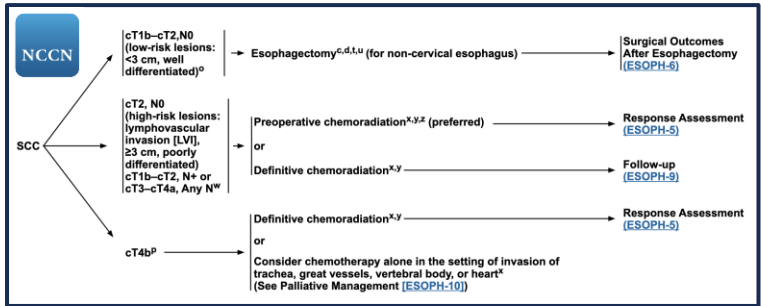
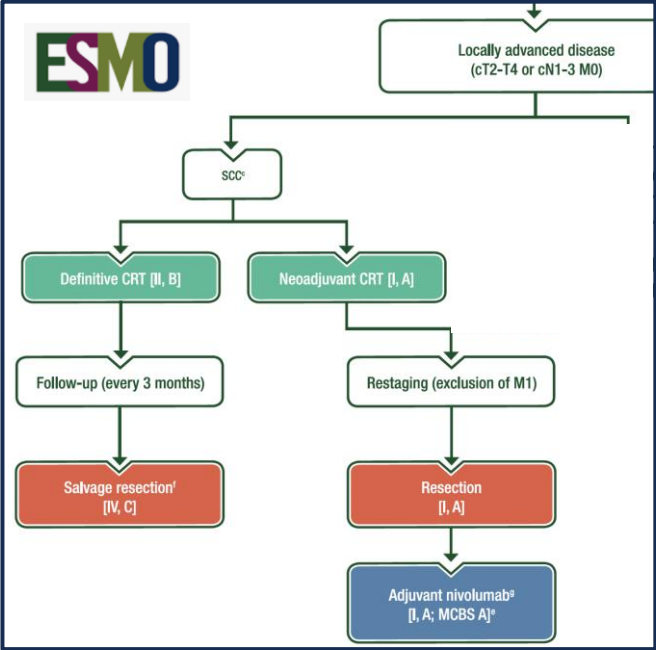


Access to advanced radiation technology.
IMRT – VMAT – SIB-RT.

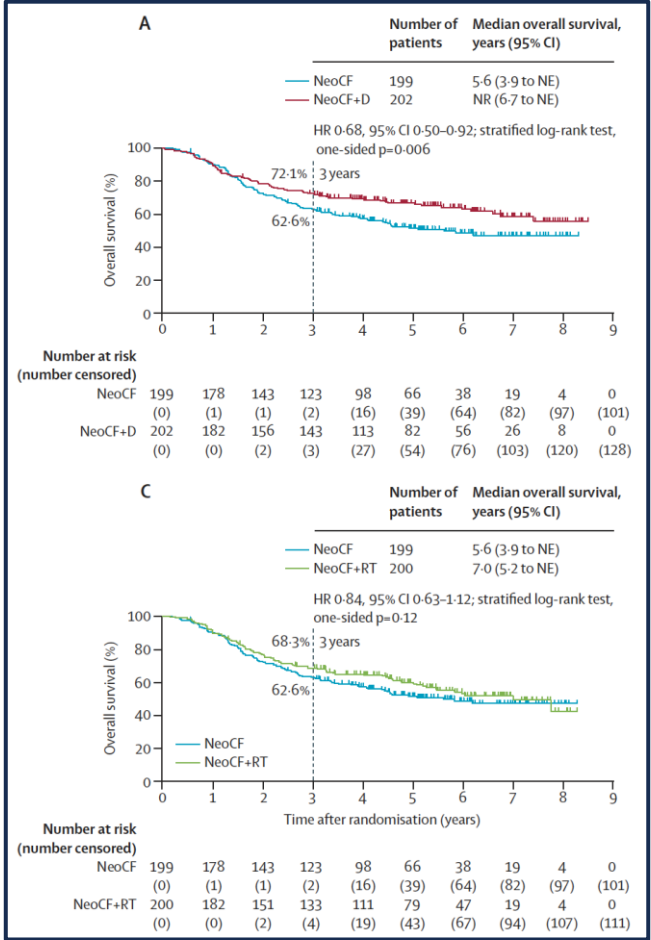
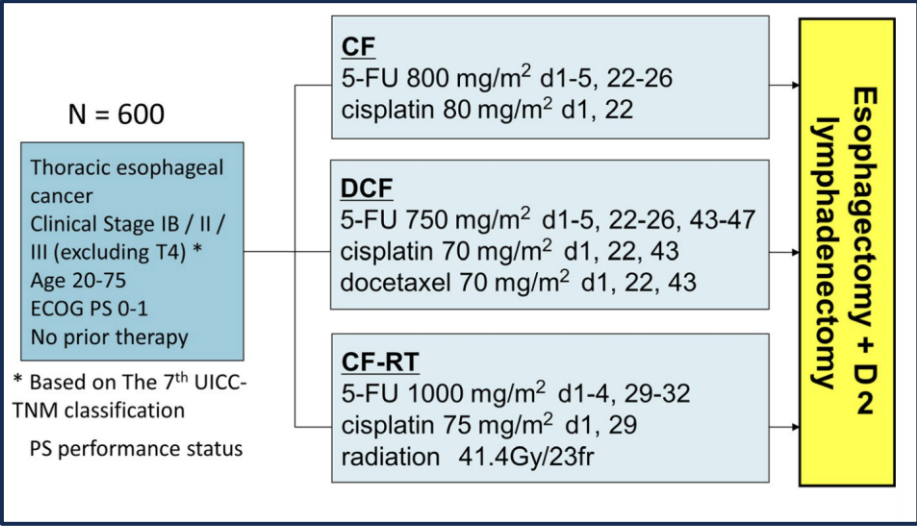


Access to high-volumen esophageal surgeons.
At least 15 esophagectomies per year.

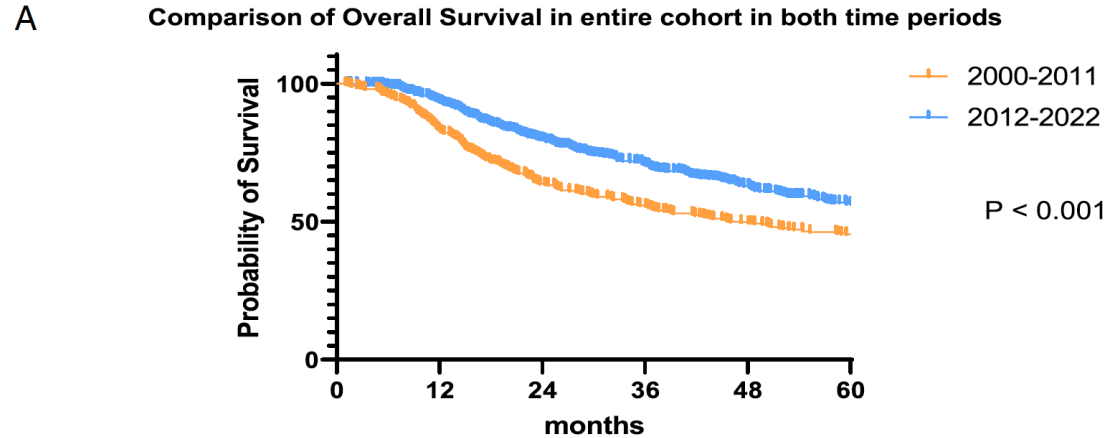
MTB: PREFERRED OPTIONS - HABITS



JCOG1109 - NExT

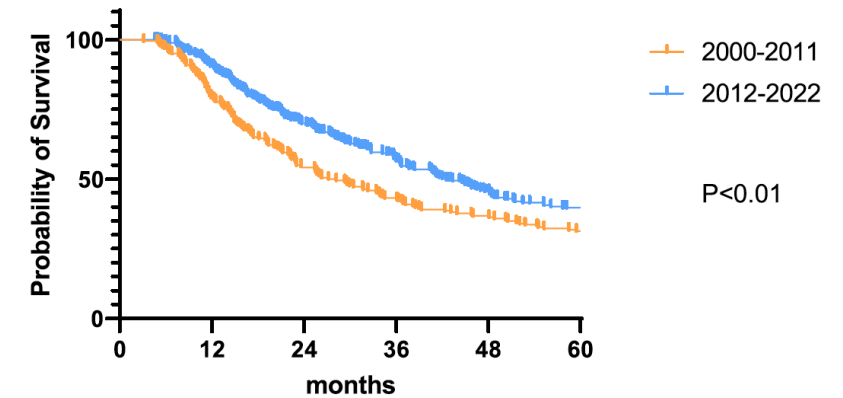


Impact of centralization on key metrics, outcomes, and patterns of care at the Irish National Centre



Survival (years)	2000-2011			2012-2022		
	No at risk	Deaths	% survival	No at risk	Deaths	% survival
1	461	76	83	784	41	94
3	381	119	56	651	130	71
5	256	46	45	359	52	57

Comparison of Overall Survival in both time periods following neoadjuvant therapy



Survival (years)	2000-2011			2012-2022		
	No at risk	Deaths	% survival	No at risk	Deaths	% survival
1	222	46	79	354	32	92
3	174	79	43	297	101	60
5	95	26	31	149	72	40

INCREASED

Endoscopic treatment

Neoadjuvant treatment

DECREASED

Operative morbidity and mortality

Recurrence rates

MTB: EVIDENCE ASSUMPTION

Figure S2. Rationale for treatment selection across treatment groups.

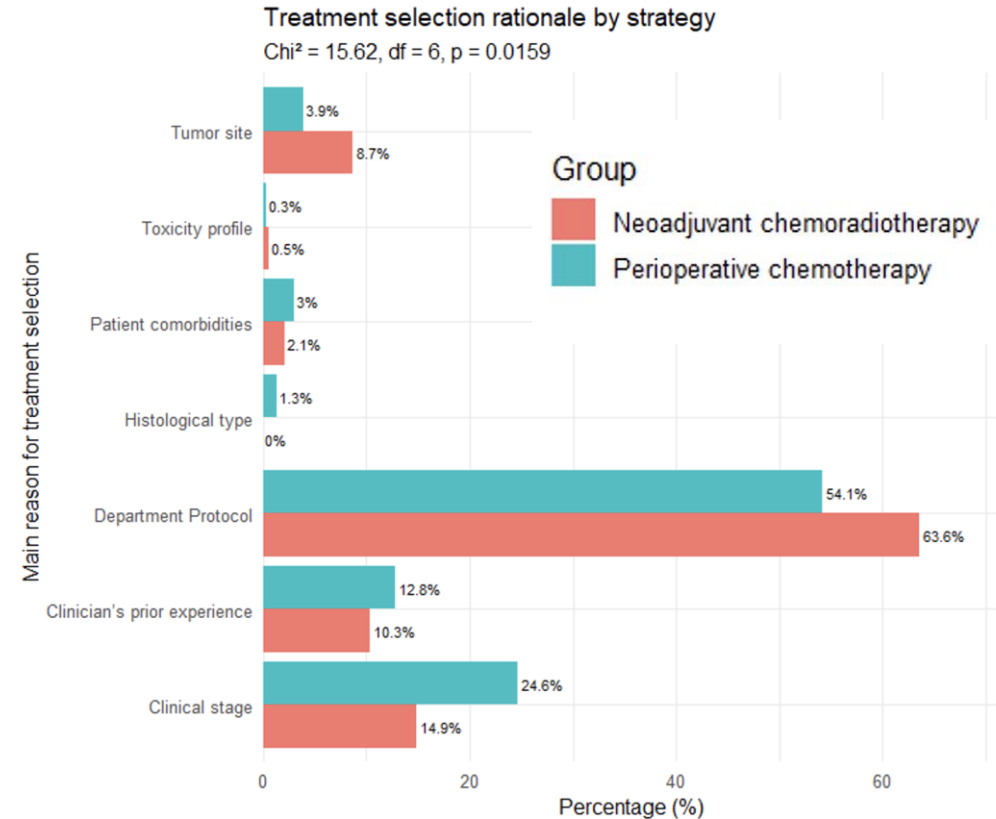
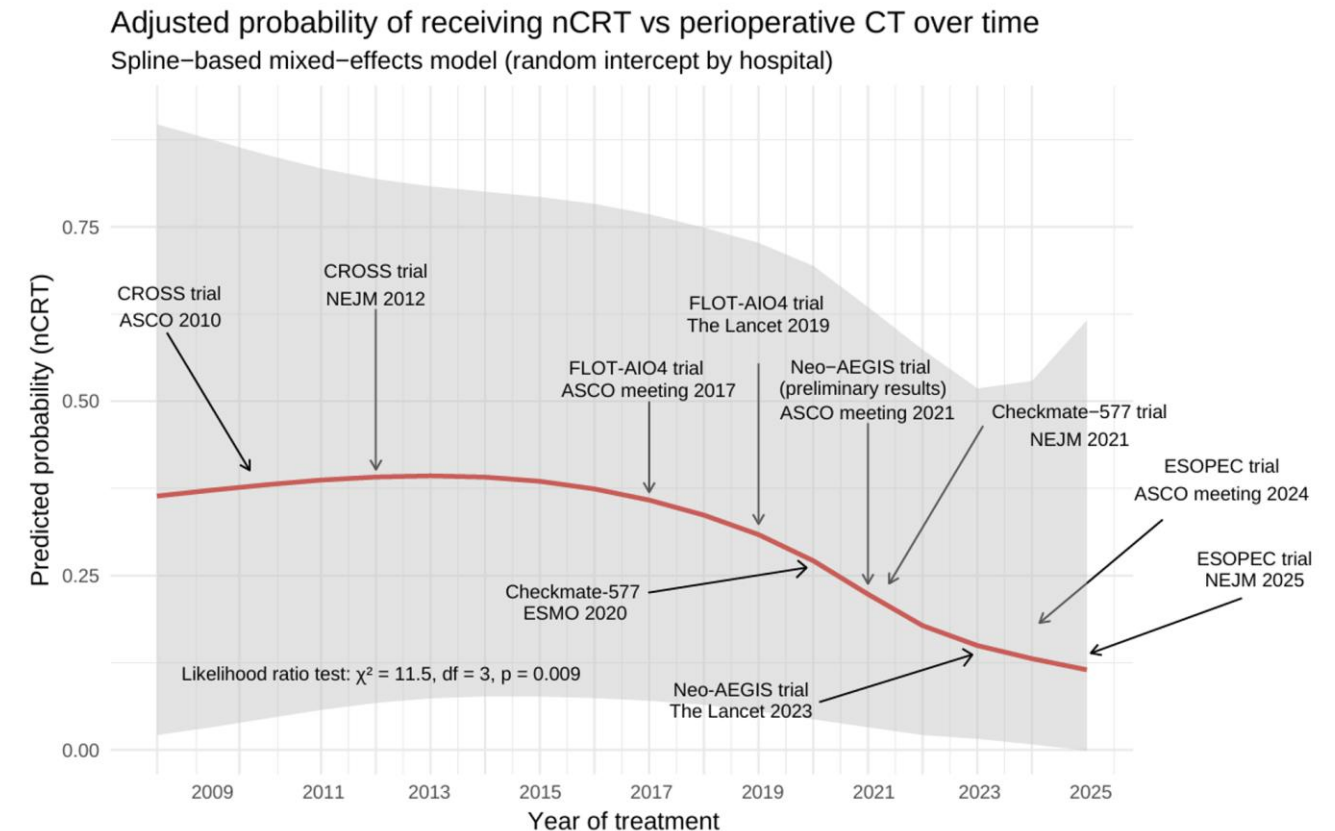
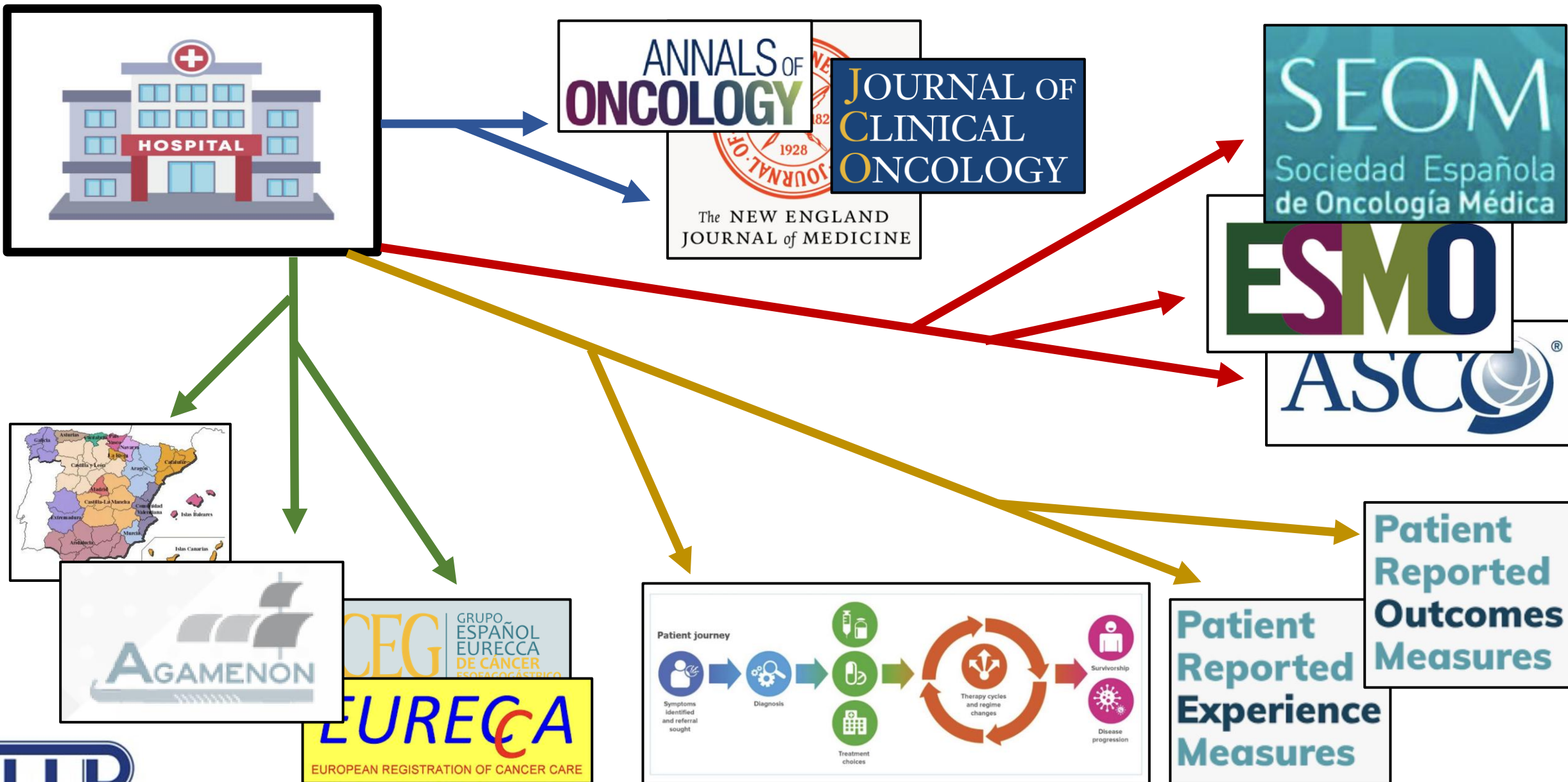


Figure S3. Adjusted probability of receiving nCRT versus perioperative CT over time based on a mixed-effects logistic regression with spline modeling of treatment year.



AGAMENON – SEOM Registry

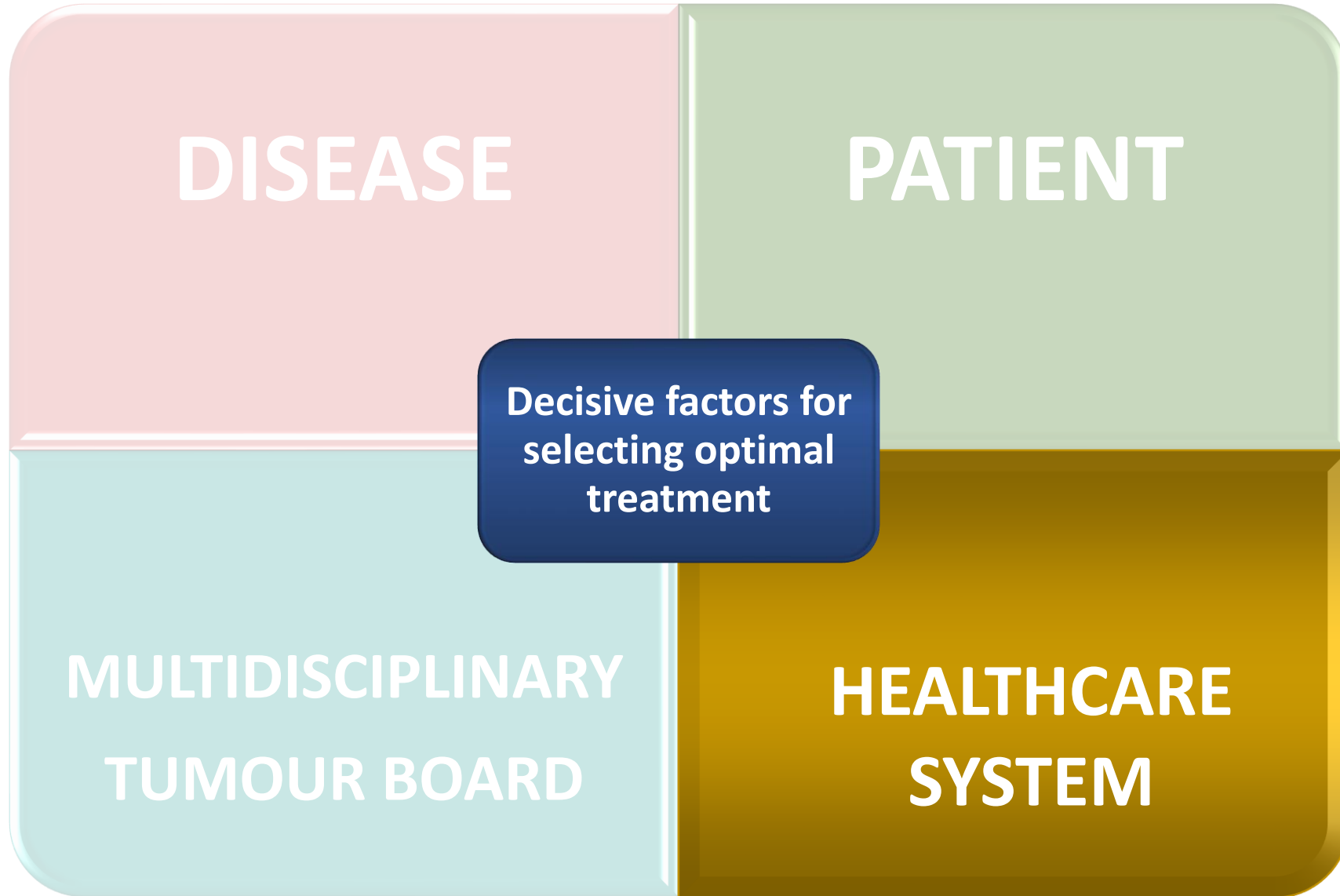
MTB: AUDIT



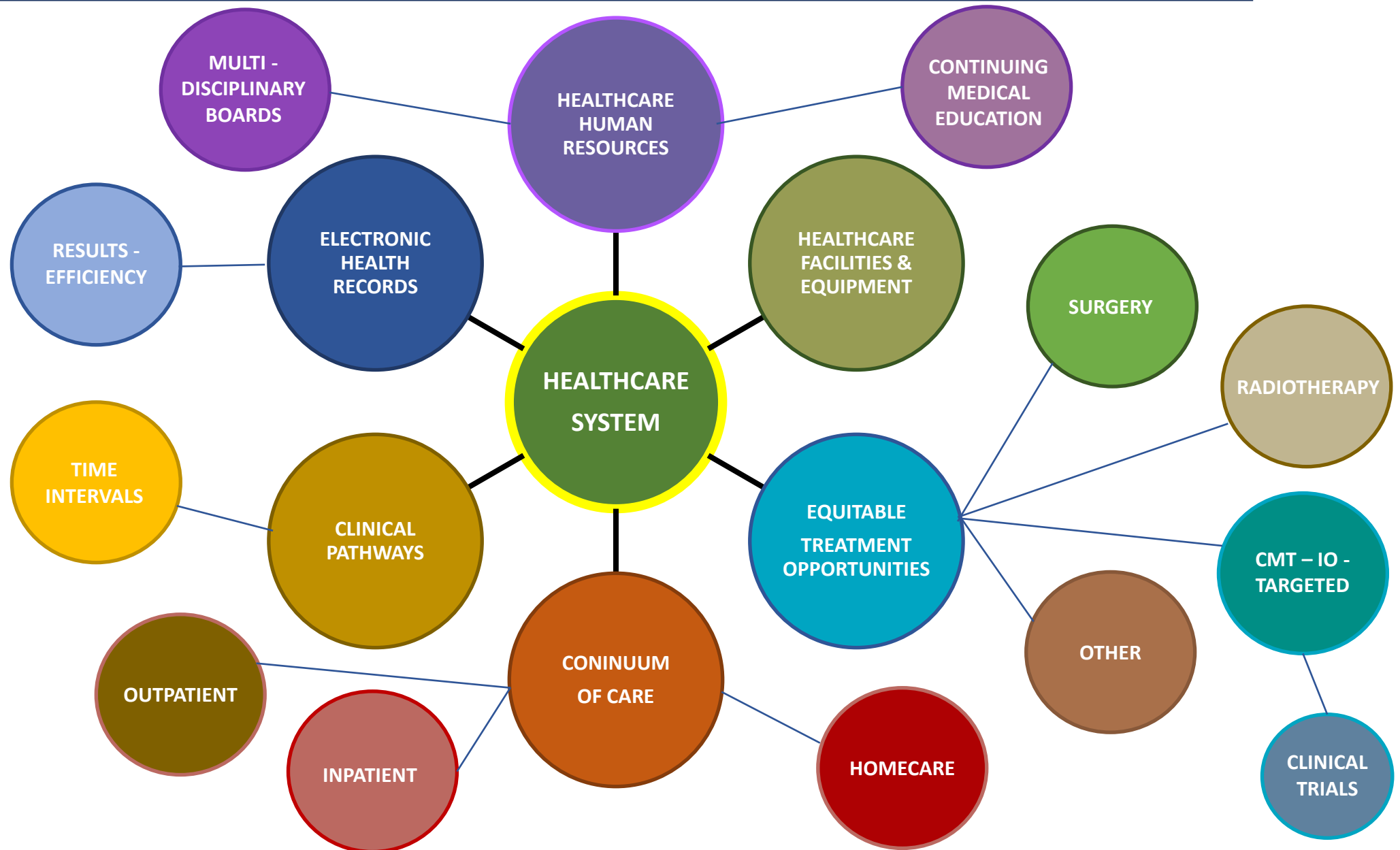
MTB: AUDIT



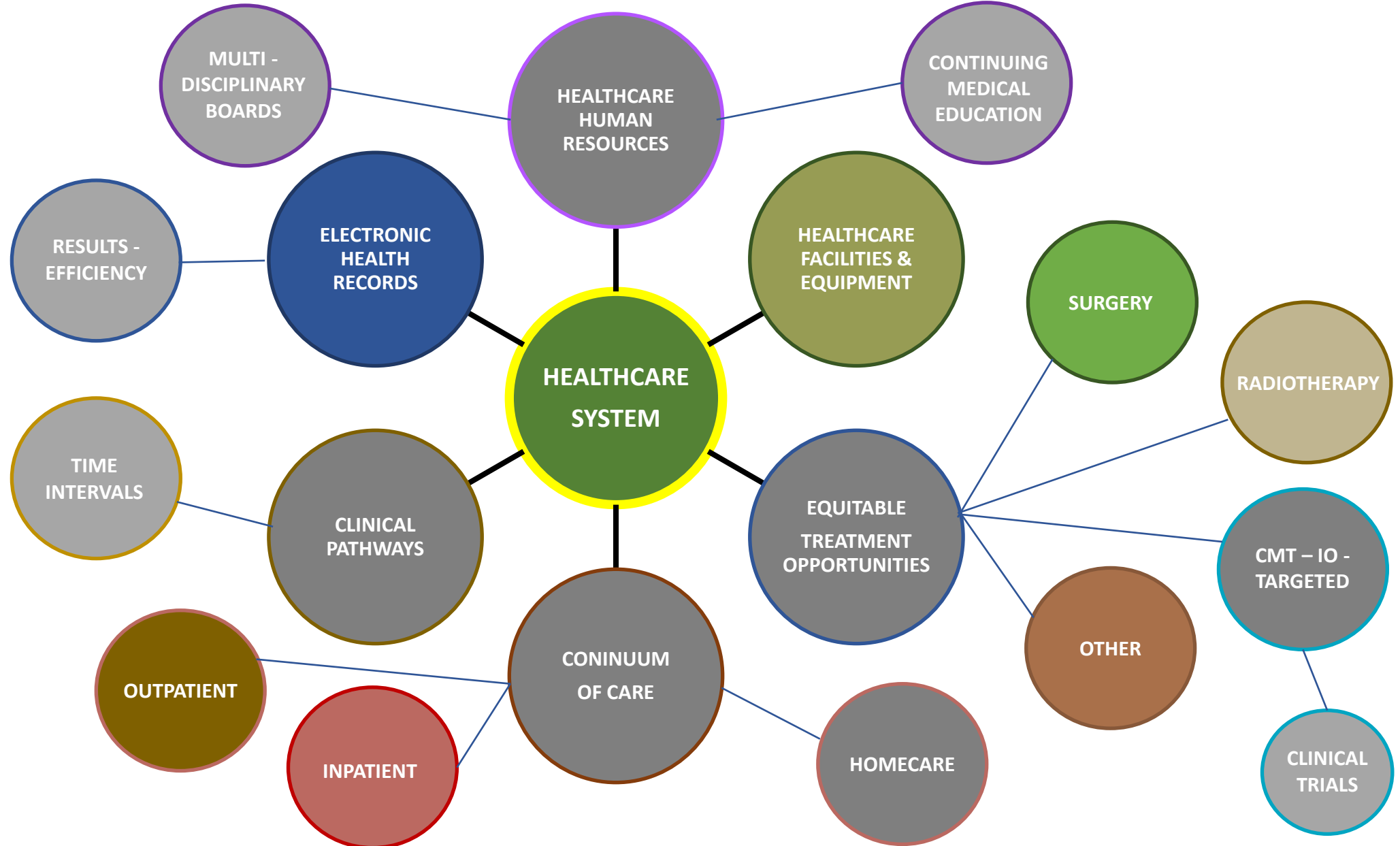
FACTORS



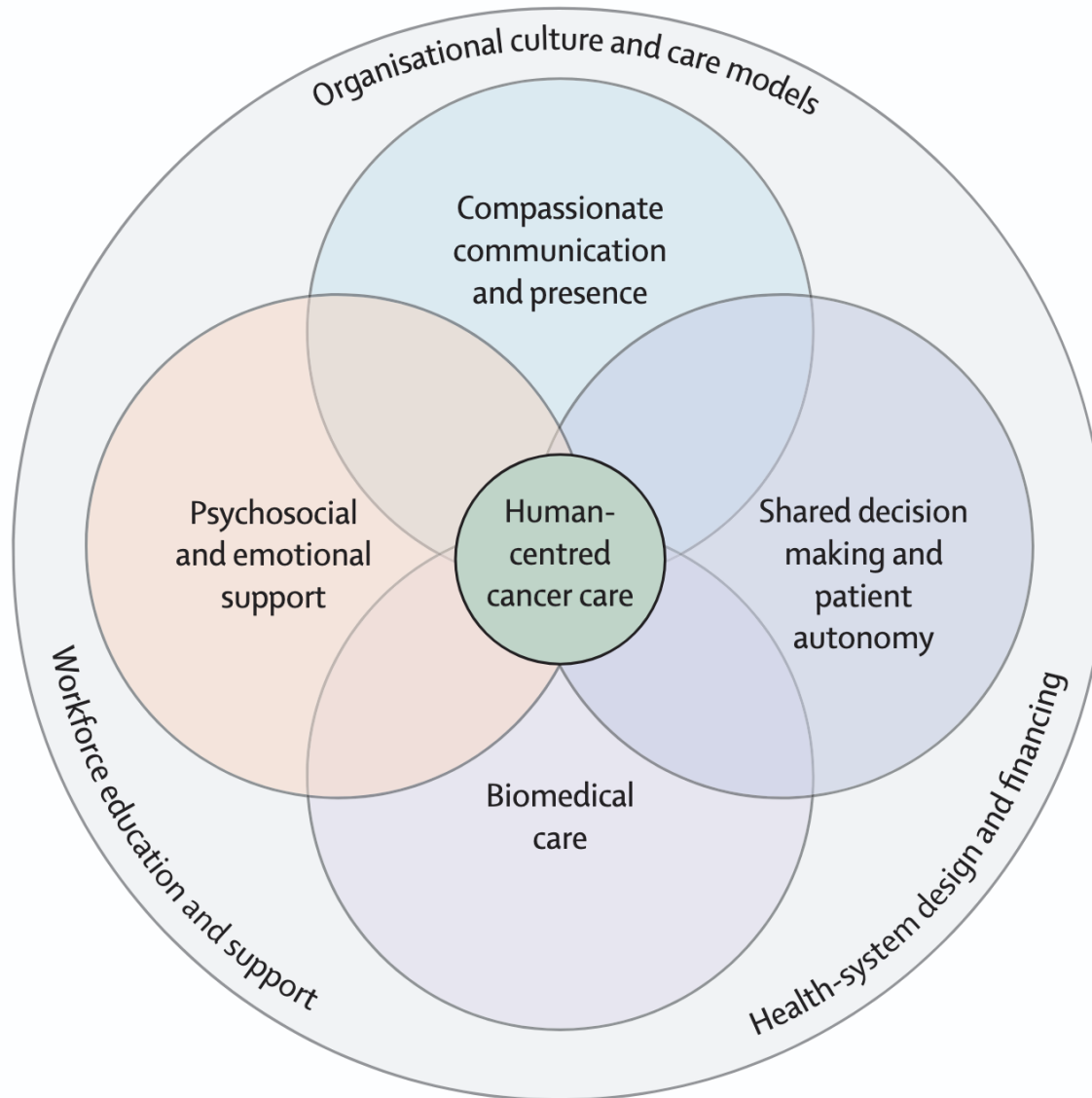
HEALTHCARE SYSTEM



SPANISH PUBLIC HEALTHCARE SYSTEM



HUMAN CRISIS IN CANCER



Lancet Oncology Commission

Amid **unprecedented scientific progress** in oncology, a growing body of evidence reveals a **parallel and profound crisis in the human experience of cancer care**.

This Commission identifies a **growing imbalance between technological innovation and the human dimensions of cancer care**. As the field has increasingly **prioritised biopharmaceutical development**, genomic precision, and market-driven efficiencies, it has often **neglected core practices that uphold dignity, alleviate suffering, and build trust**.

SISYPHUS: KEEP STRIVING



Sísifo.
Tiziano, 1548



The Agnew Clinic.
Thomas Eakins, 1889

CLOSING REMARK

A rigorous evaluation of the disease, considering patient attitude and aptitude, within an constantly updated MTB, and an enabler healthcare system, are decisive factors for selecting the optimal treatment of M0 esophageal SCC.





Optimal treatment of M0 esophageal squamous cell carcinoma:
decisive factors in selection.

¡GRACIAS!

Javier Gallego Plazas, MD, PhD.
Medical Oncology Dpt.
Hospital Gral. Univ. Elche



Vilhelm Hammershøi 1901