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BETTER MEDICINE
BEST PRACTICE

HOW TO MANAGE RESIDUAL /OLIGOMETASTATIC DISEASE FOLLOWING INDUCTION THERAPY IN SOLID TUMOURS?

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DISCLOSURES

Details of the DOI for all authors are listed at the end of this presentation

KEY MESSAGES

- Definitions and general conditions
- Goals of therapy
- Indications
- Prognostic factors
- Techniques
- Examples in different tumour types
- Conclusions

CONDITIONS FOR RESIDUAL/OLIGOMETASTATIC DISEASE INTERVENTION

Control of primary tumour (or resectable) and possibility of removal of metastatic lesions with surgical techniques or radiotherapy

MAIN THERAPEUTIC GOALS OF ADVANCED SOLID TUMOURS

- Prolongation of survival and delay of disease progression are the most primary goals of therapy in advanced disease
  - A balance with quality of life measures is increasingly considered important
- Treatment goals also include palliation of symptoms such as pain or dyspnoea, and are achieved by surgery (metastasectomy, amputation, …) and systemic therapy

AIMS FOR SURGERY OF RESIDUAL/ OLIGOMETASTATIC DISEASE

- Prolongation of durable responses (cure?) – no complete response – no cure
- Prolongation of time to progression and new tumour lesions
- Prevention of secondary resistant mutations

Metachronous (disease-free interval ≥1–2 years) organ-limited resectable metastatatic disease are managed with surgery if complete resection of all lesions is feasible

DEFINITIONS OF OLIGOMETASTATIC DISEASE

Oligometastasis	"…metastases (from tumors early in the chain of progression) limited in number and location because the facility for metastatic growth has not been fully developed and the site for growth is restricted…"
Oligometastatic disease	Solitary or few detectable metastatic lesions that are usually confined to a single organ
Oligometastases	Due to limited metastatic competence and does not occur following otherwise successful systemic treatment. New metastases in this situation, albeit even limited, is likely to have more extensive malignant capabilities that were somehow spared from eradication by therapeutic means, or from the development of resistant clones
Induced oligometastases	Occurs when widespread micrometastatic disease is mostly eradicated by systemic chemotherapy but drug resistant clones are left behind, or tumor foci is located in a site not accessed by chemotherapy
Oligorecurrence	Limited metastases in the presence of a controlled primary lesion
Sync-oligometastases	≤5 metastatic or recurrent lesions in the presence of active primary lesions
Synchronous oligometastasis	Oligometastatic disease is detected at the time of diagnosis of the primary tumor, therefore there is an active primary tumor
Metachronous oligometastasis	Development of oligometastatic disease after treatment of the primary tumor; interval for classification of metachronous versus synchronous is not standardized; between Controlled primary lesion except for concomitant primary and distant recurrence
Oligoprogression	Progression of a limited number of metastatic deposits, while remaining metastases are controlled with systemic therapy
Oligometastasis (specific to prostate cancer)	Rising PSA following primary therapy, with oligometastasis on imaging, in whom local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) is required to defer initiation of ADT
Oligometastasis (specific to prostate cancer)	Castrate resistant prostate cancer with a rising PSA and oligometastasis on imaging, in whom local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) may allow deferral of ADT

OLIGOMETASTATIC DISEASE

- Good prognostic factors → Surgery is standard
- Bad prognostic factors (e.g. short term disease-free interval) → Systemic therapy is standard

OLIGOMETASTATIC DISEASE

- Solid cancer not sensitive to systemic therapy (e.g. chondrosarcoma), long-term disease-free interval → Local therapy only standard
- Solid cancer highly sensitive to systemic therapy, even short term disease-free interval, local recurrence etc. → Systemic therapy first standard

TECHNIQUES

- Classic or « minimally » invasive surgery
- Radiofrequency ablation (RFA)
- Cryoablation
- Laser ablation
- Perfusion techniques, including HIPEC
- Embolisation
- Radiosurgery, stereotactic radiotherapy

THE MOST COMMON TYPES OF SOLID TUMOURS FOR LOCAL INTERVENTION IN RESIDUAL/OLIGOMETASTATIC DISEASE ARE:

Colorectal cancer

Lung cancer

Breast cancer

Gastric cancer

Melanoma

Sarcoma

Renal-cell carcinoma

Prostate cancer

Ovarian cancer

INDICATIONS FOR LOCAL THERAPY OF RESIDUAL/OLIGOMETASTATIC DISEASE

Limited tumour burden(oligometastatic)

Resectable – based on imaging examination (R0 resection potentially feasible)

Longer disease-free interval

Good performance status of the patient (0 - 2 WHO)

Expected survival > 3 months

MAJOR PROGNOSTIC FACTORS

- Radicality of surgery
- Number of metastases
- Disease-free interval (DFI)
- LongTDT (tumour-volume doubling time)
- Limited to one organ versus multiple organs
- Synchronous local recurrence

OLIGOMETASTATIC MELANOMA

1st Author, Year	Strength of evidence-based on study design / endpoint	Prospective (P) or retrospective (R)	Sample size	Definition-Oligo metastases	Therapy	Endpoint	Conclusion
Essner, 2004	3i /A	R	877	1 met	Curative surgery	5yr OS- 29 mths if mets 1 site, 16 mths if mets 2-3 sites, 14 mths if met ≥4 sites. 5yr OS- 17% disease-free if distant mets in <36 mths, 30% if >36 mths	Patients with limited mets should be considered for curative resection
Knisely, 2012	3iii /A	R	77	Brain mets treated with SRS	SRS to brain mets, then 35% of group received ipilimumab	MOS- 21.3 mths in ipilimumb group vs 4.9 mths in no-ipilimumb group. 2yr OS- 47% in ipilimumab group and 19.7% in no-ipilimumb group	Survival of patients with melanoma and brain mets managed with ipilimumb + SRS can exceed expected 4-6 mths

Mets, metastases; OS, overall survival; SRS, stereotactic radiosurgery; MOS, median overall survival.
Reys DK, *et al.* Oncotarget 2015;6(11);8491–524.

OLIGOMETASTATIC RENAL CELL CARCINOMA

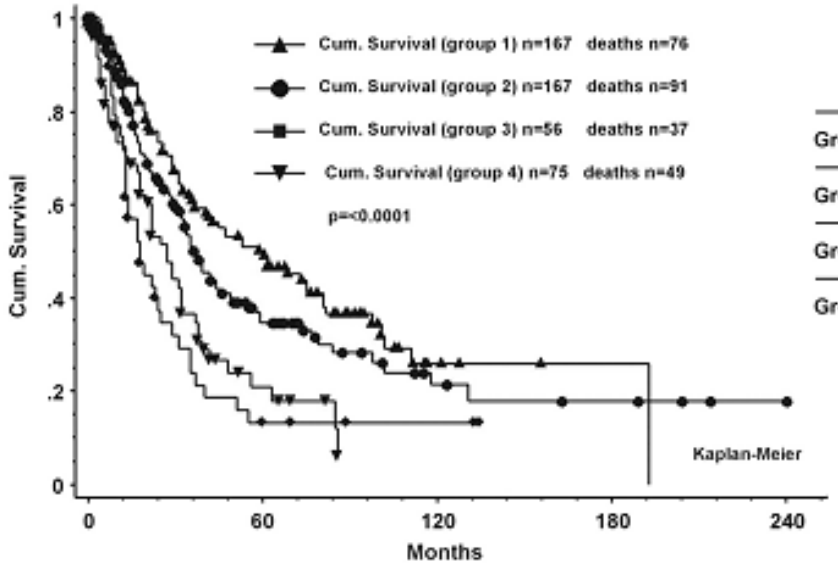
1st Author, Year	Strength of evidence-based on study design / endpoints	Prospective (P) or retrospective (R)	Sample size	Definition- Oligo metastases	Therapies	Endpoints	Conclusion
Mickisch, 2001	1ii /A	P	85	N/A – patients identified as having metastatic RCC	Surgery + interferon OR interferon only	TTP (5 vs 3 mths) + MOS (17 vs 7 mths) in surgery + interferon vs interferon only	Radical nephrectomy before interferon-based immunotherapy may delay TTP and improve survival in mRCC
Flanigan, 2001	1ii /A	P	241	N/A – patients identified as having metastatic RCC	Surgery followed by interferon OR interferon only	Surgery followed by interferon MOS- 11.1 mths vs interferon alone MOS- 8.1 mths	Nephrectomy followed by interferon had longer survival
Bang, 2012	3iii /A	R	27	Localised soft tissue mass <7 cm + ≤5 lesions in 1 organ	Cryoablation	5yr OS- 27%	Multiple cryoablation of OM RCC associated with low morbidity and low recurrence with apparent increased OS
Ranck, 2013	3ii /A	R	18	Limited metastatic disease	SBRT: 3 fractions or 10 fractions	2yr OS- 85%	SBRT produces promising lesion control with minimal toxicity
Thibault, 2014	3iii /A	R	13	<5 spinal mets	SBRT	1yr OS- 83.9% in OM RCC (n=13) vs 52.5% in non-OM RCC (n=24)	Multivariate analysis identified OM RCC as a prognostic factor for survival. OM RCC may benefit the most from aggressive local therapy

TTP, time to progression, mRCC, metastatic renal cell carcinoma, MOS, median overall survival; OM, oligometastatic; OS, overall survival; SBRT, stereotactic body radiation therapy; Mets, metastases.

Reys DK, *et al.* Oncotarget 2015;6(11);8491–524

THE ROLE OF SURGERY AND ABLATIVE RADIOTHERAPY IN OLIGOMETASTATIC BREAST CANCER*

Complete resections according to risk groups



	5 - year surv.	5 - year at risk	10 - year surv.	10 - year at risk	15 - year surv.	15 - year at risk	median
Group 1 (no risk factor)	50%	47	26%	5	26%	1	59 m.
Group 2 (1 risk factor)	35%	31	21%	8	18%	4	36 m.
Group 3 (2 risk factors)	13%	4	13%	2			18 m.
Group 4 (incomplete res.)	18%	7					25 m.

*Salama JK, *et al.*
Friedel G, *et al.* Eur J Cardiothorac Surg 2002;22:335-344.
Actuarial outcomes for metastatic breast cancer patients treated with surgical resection of pulmonary metastases. Patients are stratified based on risk groups. Group I: complete resection, disease-free interval (DFI) ≥36 months, solitary metastasis 5-year survival 50%, 10- and 15-year survival 26% with a median survival 26% with a median survival of 59 months. Group II: complete resection, DFI <36 months or multiple metastases 5-year survival 35%, 10-year survival of 21% and 15-year survival of 18% with a median survival of 36 months. Group III: complete resection, DFI <36 months and multiple metastases survival after 5 and 10 years 13% with a median survival of 25 months. Group IV: incomplete resection, 5-year survival of 18% with a median survival of 25 months. The differences between the groups I and II compared to groups III and IV are statistically significant (log-rank P<0.001, $\chi^2 = 30.014$).

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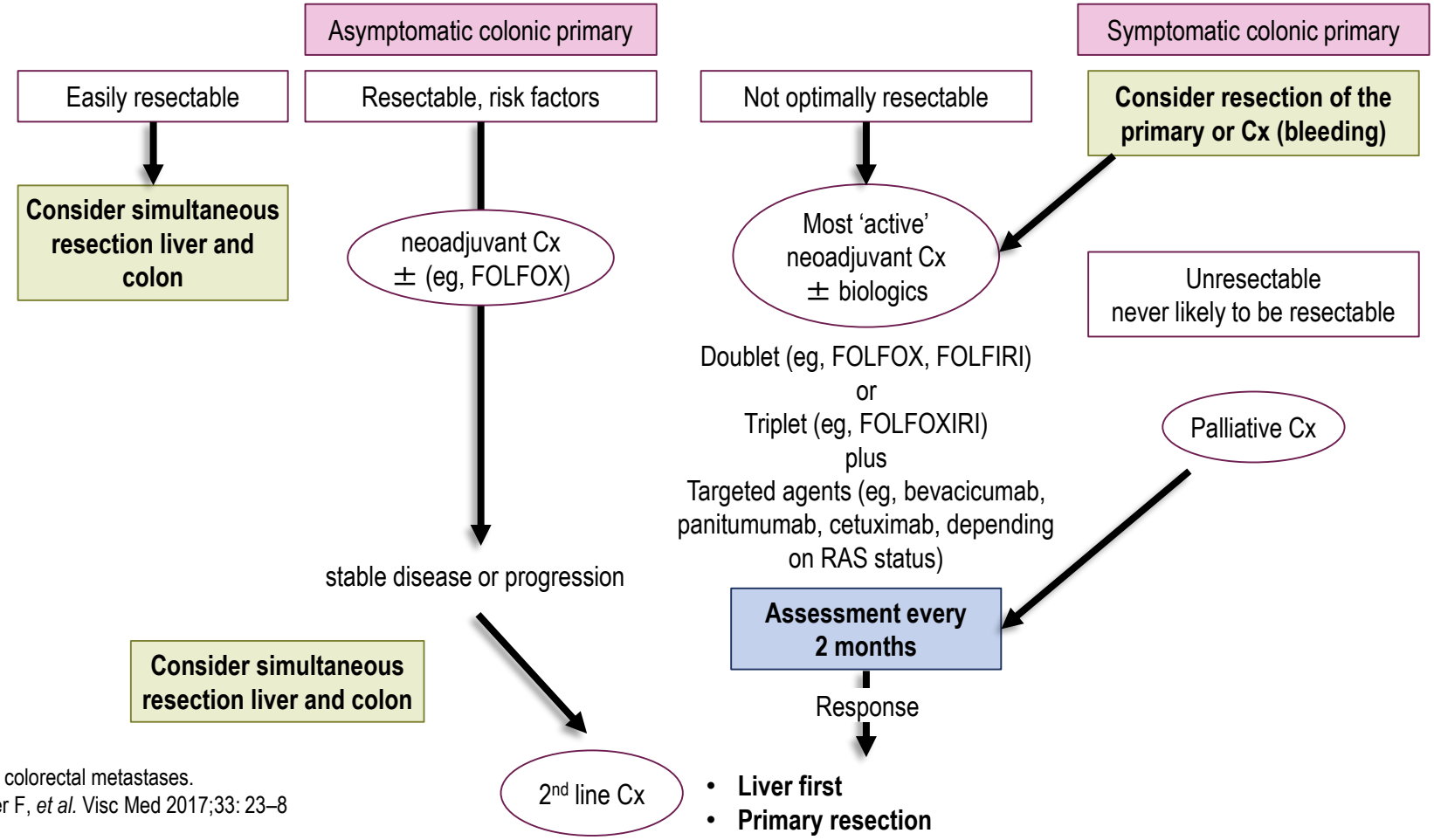
OLIGOMETASTATIC DISEASE IN COLORECTAL CANCER

How to proceed?



CLM, colorectal metastases.

Aigner F, *et al.* Visc Med 2017;33: 23–8

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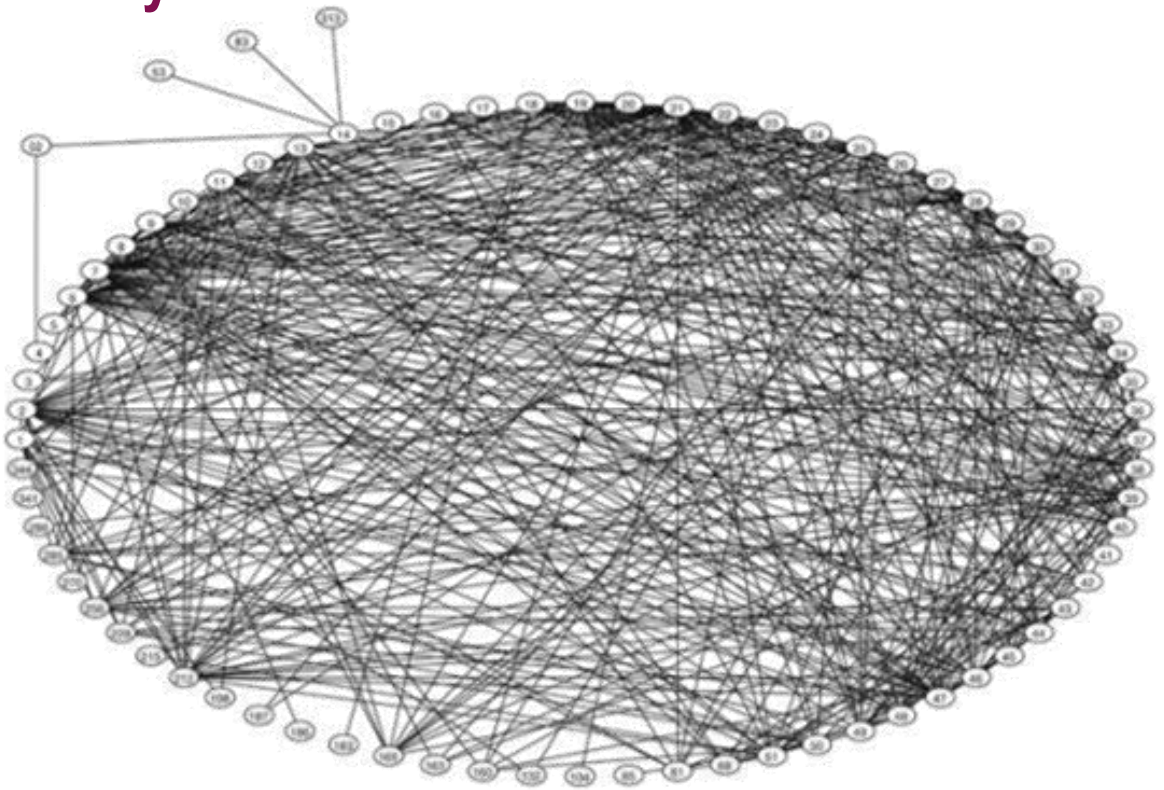
LEVEL OF EVIDENCE

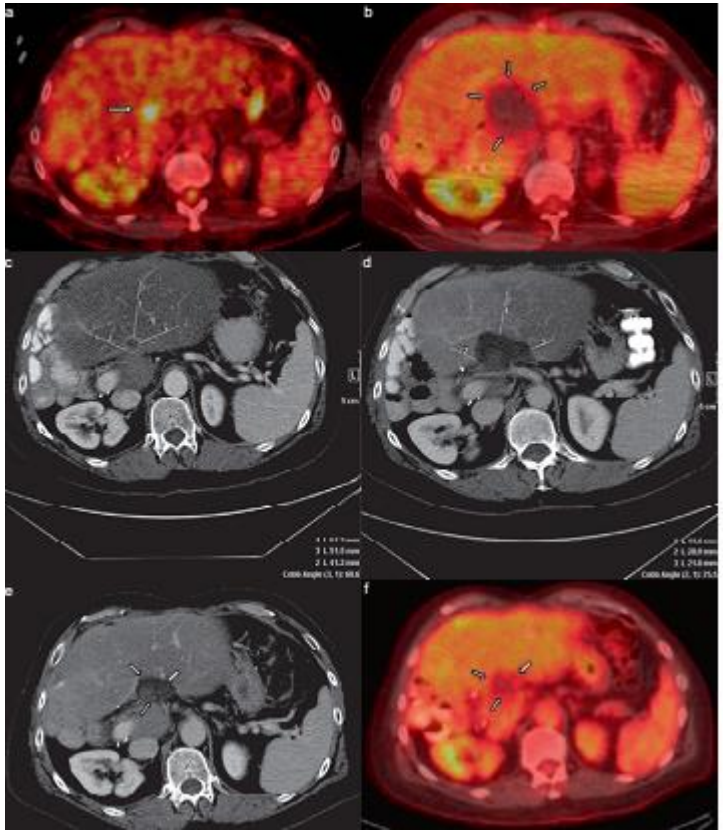
Clinical reports of pulmonary metastasectomy for colorectal cancer: **a citation network analysis**

4 studies not in favour of metastasectomy



THERMAL ABLATION

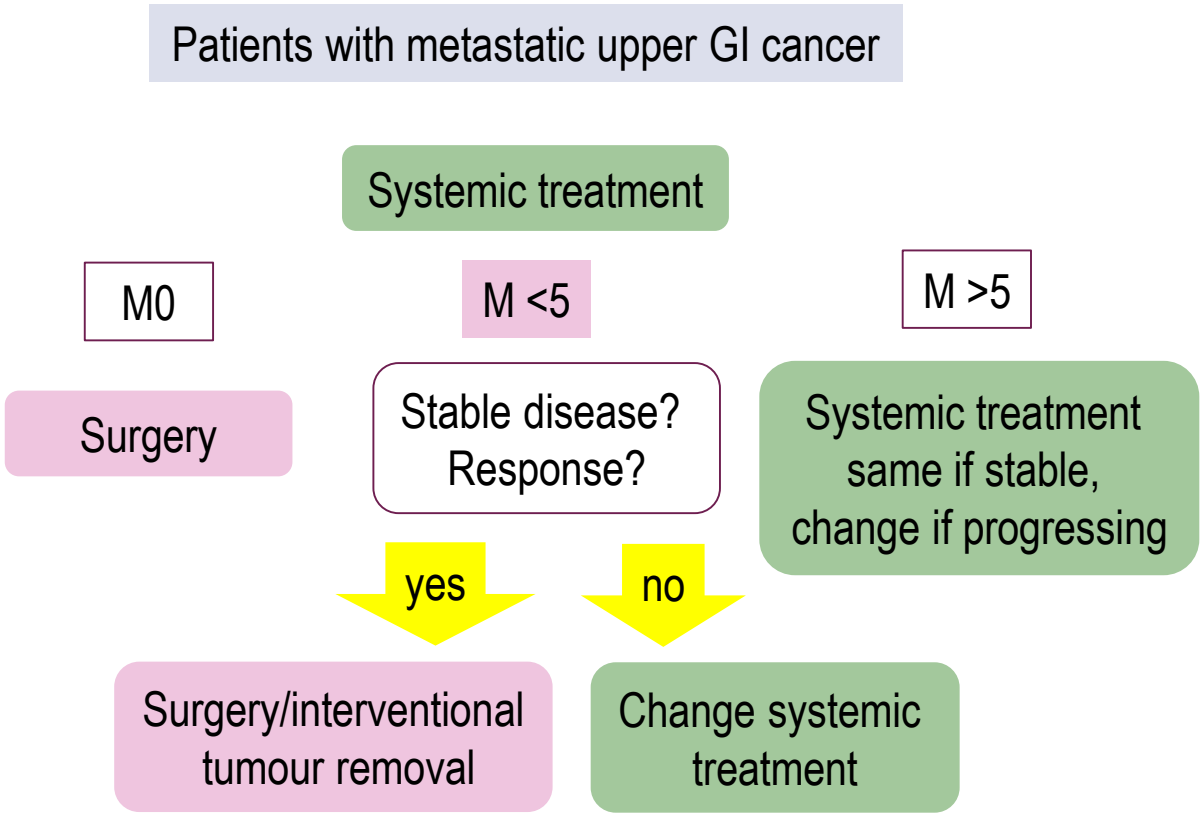
In the management of colorectal cancer patients with oligometastatic liver disease



Petre EN, *et al.* Visc Med 2017; 33: 62–8. With permission from S. Karger AG, Basel

OLIGOMETASTATIC DISEASE IN UPPER GASTROINTESTINAL CANCER

How to proceed?



Chiapponi C, *et al.* Visc Med 2017; 33: 31-34.

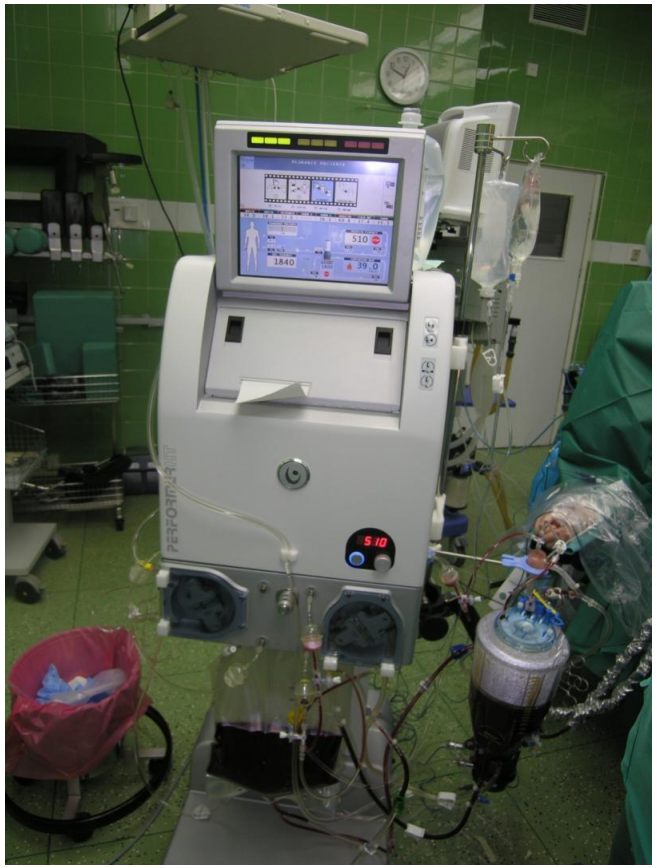
PROGNOSTIC SCORE AFTER RESECTION OF LIVER METASTASES

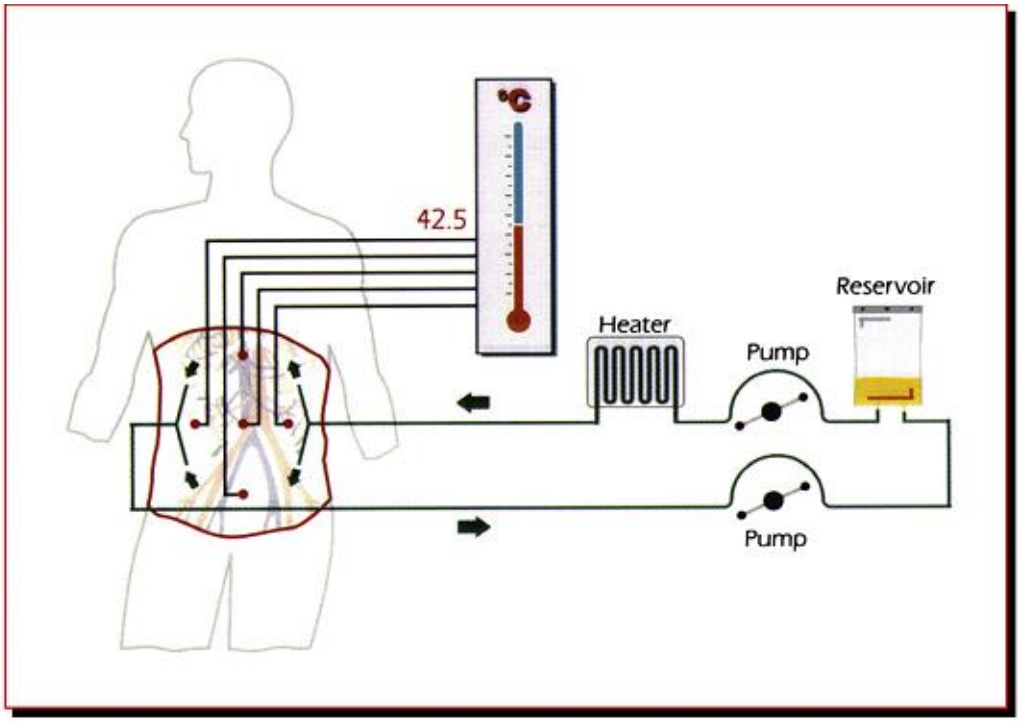
CLINICAL RISK SCORE FOR TUMOUR RECURRENCE						
	Survival %					
Score	1-yr	2-yr	3-yr	4-yr	5-yr	Median (mo)
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumour, Size >5 cm, CEA >200 ng/mL

Fong Y, *et al.* Ann Surg 1999;230(3):309–18; discussion 318–21.

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)



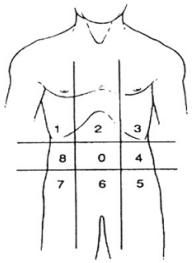


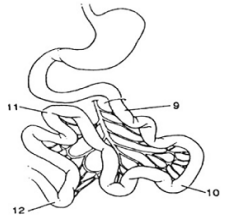
CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

In the management of peritoneal surface malignancies of colonic origin: A consensus statement

Completeness of cytoreduction (CCR) score	
Stage	Description
CCR 0 No residual	No peritoneal seeding exposed during the complete exploration (complete cytoreduction)
CCR 1 <2.5 mm	Diameter of tumour nodules persisting after cytoreduction (complete cytoreduction)
CCR 2 >2.5 mm <2.5 cm	Diameter of tumour nodules persisting after cytoreduction (incomplete cytoreduction, moderate residual disease)
CCR 3 >2.5 cm	Diameter or a confluence of unresectable tumour nodules at any site within abdomen (incomplete cytoreduction, gross residual disease)

Peritoneal Cancer Index (PCI) staging system for peritoneal carcinomatosis





Regions		Lesion Size
0	central	_____
1	Right upper	_____
2	Epigastrium	_____
3	Left upper	_____
4	Left flank	_____
5	Left lower	_____
6	Pelvis	_____
7	Right lower	_____
8	Right flank	_____
9	Upper jejunum	_____
10	Lower jejunum	_____
11	Upper ileum	_____
12	Lower ileum	_____
	PCI	0-39

Lesion SizeScore (the largest implants scored in each regions)

- **LS 0** No tumor seen
- **LS 1** ≤ 0.5 cm
- **LS 2** > 0.5 cm to ≤ 5.0 cm
- **LS 3** > 5 cm or confluence

The abdomen and the pelvis are divided into 12 regions. The lesion sizes of the largest implants are scored (0 through 3) in each abdominopelvic region. They can be summed as a numerical score, which varies from 1 to 39.

Esquivel J, *et al*. Ann Surg Oncol 2007;14(1):128–33.

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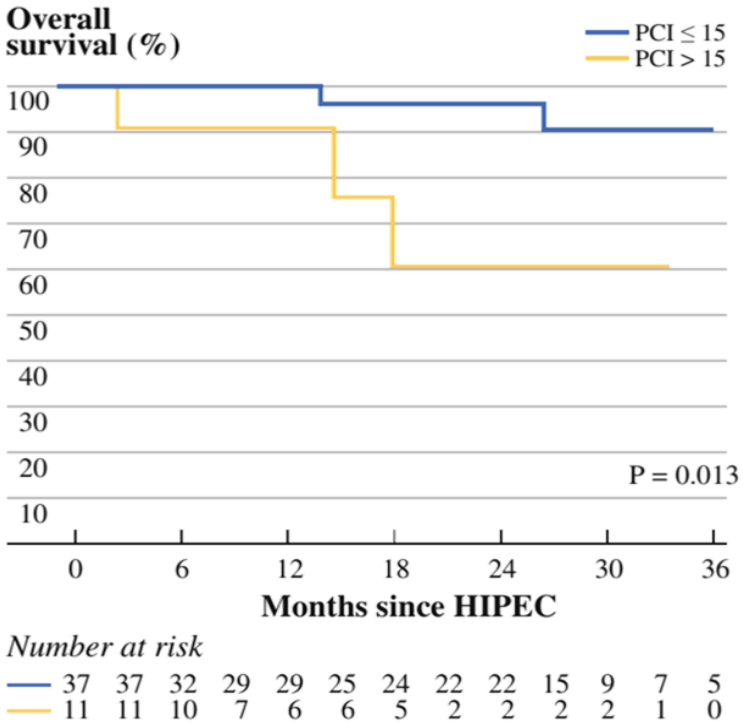
CURRENT STATUS OF CYTOREDUCTIVE SURGERY

With hyper thermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer

Correlation between PCI and survival in patients with PC from colorectal cancer treated with CRS and HIPEC

Ref	PCI	Median survival (mo)	Survival rates (%)		
			1	2	3
Pestieau and Sugarbaker, 2000	≤10	48.0			50
	11–20	24.0			20
	>20	12.0			0
Glehen, *et al.* 2004	<13	34.8	92	50	33
	≥13	14.4	62	22	11
Kecmanovic, *et al.* 2005	≤13	16.8			
	>13	6.9			
Yan, *et al.* 2008	<10	nr	95	71	
	≥10–<20	29	63	18	
	≥20	27	80	0	
Elias, *et al.* 2010	1–6	40.0		55	44
	7–12	29.0		39	22
	13–19	25.0		40	29
	>19	18.0		18.5	7
Cavaliere, *et al.* 2011	<11	23.0 (31)			
	11–20	16.0 (19)			
	>20	11.0 (14)			



Reprinted by permission from Springer Nature: Ann Surg Oncol. The Treatment of Peritoneal Carcinomatosis of Colorectal Cancer with Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) with Oxaliplatin: A Belgian Multicentre Prospective Phase II Clinical Study, Hompes D, *et al.* Copyright 2012

OVERALL SURVIVAL

According to number of CLM and the PCI after surgical treatment with curative intent

- N=37 patients with PC and LM matched with n=61 patients with PC alone
- Mean follow-up 36 months

	Patients with PC	Patients with LM	P-value
3-year OS (months)	40	66	0.04
3-year DFS (months)	6	27	0.001

	Patients with low PCI (<12) and no LM	Patients with low PCI (<12) and 1 or 2 LM	Patients with high PCI (≥12) or patients with ≥3 LMs
OS (months)	76	40	27

CYTOREDUCTIVE SURGERY AND HYPER THERMIC INTRAPERITONEAL CHEMOTHERAPY

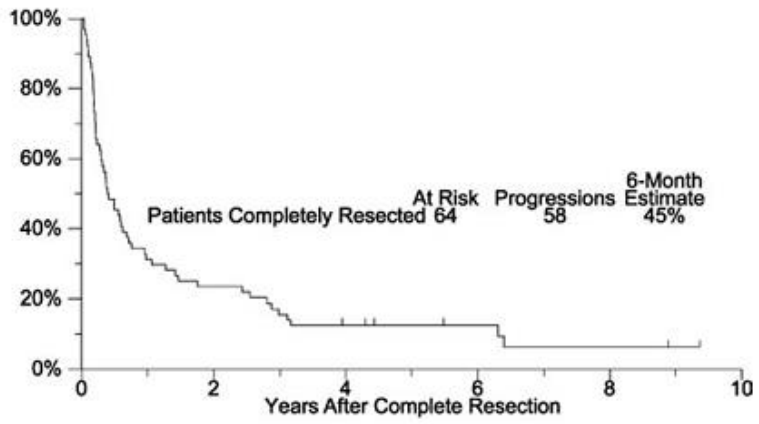
Improves survival of patients with peritoneal carcinomatosis from gastric cancer: Final results of a Phase III randomised clinical trial

Investigator	Year of publication	n	PCI cut-off	Significance
Boerner *et al.*	2016	38	10	Median survival time 17.2 months (95% CI 10.1-24.2 months)
Yang *et al.*	2010	30	20	Median survival time PCI < 20 was 27.7 months (95% CI 15.2-40.3 months) and high PCI > 20 was 6.4 months (95% CI 3.8-8.9 months) (p=0-000)
Glehen *et al.*	2010	159	12	Mean PCI was 9.4 (SD: 7.7)
Yonemura *et al.*	2010	95	<6	Median survival time with PCI <6 was 33.6 months and PCI >6 was 13.2 months
Canbay *et al.*	2014	194	<6	
Coccolini *et al.*	2015	748	12	Meta-analysis

PCI, peritoneal carcinomatosis index

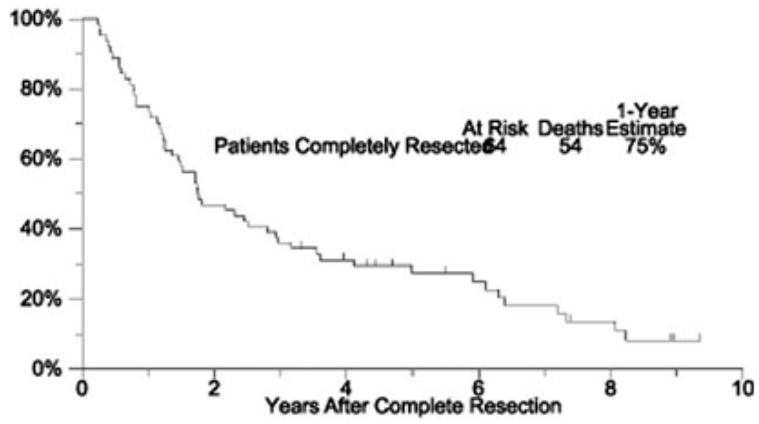
Rau B, *et al.* Visc Med 2017;33:42–46

A PHASE 2 TRIAL OF COMPLETE RESECTION FOR STAGE IV MELANOMA



6-month: 45% (95% CI: 33% - 58%)
1-year: 31% (95% CI: 20% - 43%)
2-year: 23% (95% CI: 13% - 34%)
3-year: 16% (95% CI: 7% - 25%)
4-year: 13% (95% CI: 4% - 21%)

Kaplan-Meier estimates of relapse-free survival (RFS) for those patients who were completely resected of all disease are shown. RFS was defined as the time from the date of complete resection until the date of disease relapse or death due to any cause. Patients last known to be alive and without disease relapse were censored at the date of last contact and are marked on the curve with a tic representing the last follow-up time. RFS at specified time points with 95% confidence intervals are presented at the bottom of the figure.



1-year : 75% (95% CI : 64% - 86%)
2-year: 47% (95% CI: 35% - 59%)
3-year: 36% (95% CI: 24% - 48%)
4-year: 31% (95% CI: 20% - 42%)

Kaplan-Meier estimates of overall survival (OS) for those patients who were completely resected of all disease are shown. OS was defined as the time from the date of complete resection until the date of death due to any cause. Patients last known to be alive were censored at the date of last contact and are marked on the curve with a tic representing the last follow-up time. OS at specified time points with 95% confidence intervals are presented at the bottom of the figure.

METASTASECTOMY FOR DISTANT METASTATIC MELANOMA

Analysis of data from the first multicentre selective lymphadenectomy trial (MSLT-I)

Results. Of 291 patients with complete data for stage IV recurrence, 161 (55 %) underwent surgery with or without SMT. Median survival was 15.8 versus 6.9 months, and 4-year survival was 20.8 versus 7.0 % for patients receiving surgery with or without SMT versus SMT alone ($p < 0.0001$; hazard ratio 0.406). Surgery with or without SMT conferred a survival advantage for patients with M1a (median > 60 months vs. 12.4 months; 4-year survival 69.3 % vs. 0; $p = 0.0106$), M1b (median 17.9 vs. 9.1 months; 4-year survival 24.1 vs. 14.3 %; $p = 0.1143$), and M1c (median 15.0 vs. 6.3 months; 4-year survival 10.5 vs. 4.6 %; $p = 0.0001$) disease. Patients with multiple metastases treated surgically had a survival advantage, and number of operations did not reduce survival in the 67 patients (42 %) who had multiple surgeries for distant melanoma.

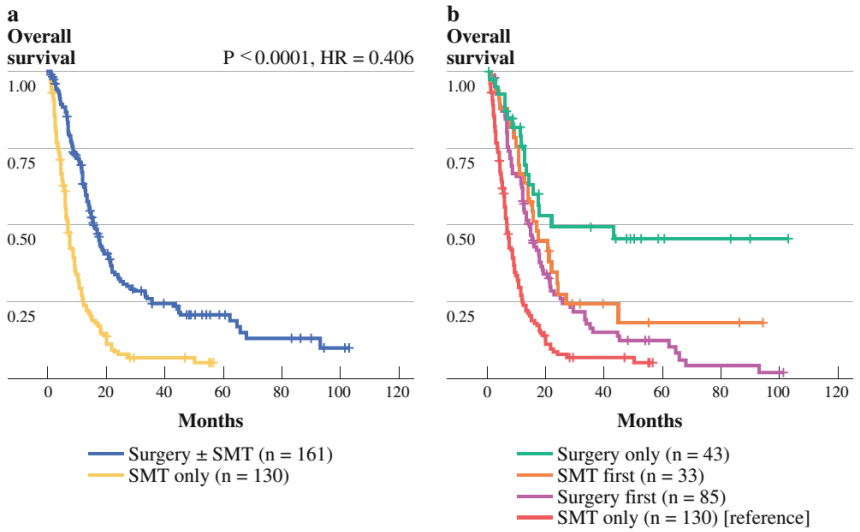


FIG. 1 **a** Overall survival for patients whose recurrent stage IV melanoma was treated with surgery with or without SMT ($n = 161$, median survival 15.8 months, 4-year survival 20.8 %) versus SMT alone ($n = 130$, median survival 6.9 months, 4-year survival 7.0 %). **b** Overall survival for patients by treatment received: surgery only ($n = 43$, median survival 22.1 months, 4-year survival 45.7 %), SMT followed by surgery ($n = 33$, median survival 17.1 months, 4-year survival 18.2 %), surgery followed by SMT ($n = 85$, median survival 14.7 months, 4-year survival 12.3 %), or SMT alone ($n = 130$, median survival 6.9 months, 4-year survival 7.0 %); $p < 0.0001$

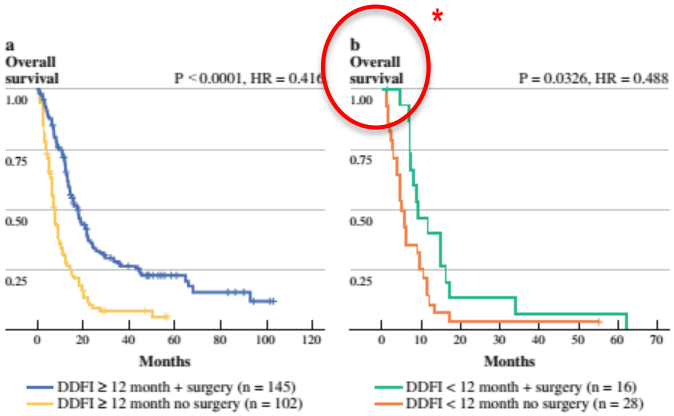


FIG. 2 Overall survival based on DDFI. Overall survival is compared for patients with **a** long (≥12 months) and **b** short (<12 months) DDFI by use of surgery vs. SMT alone for treatment of stage IV melanoma

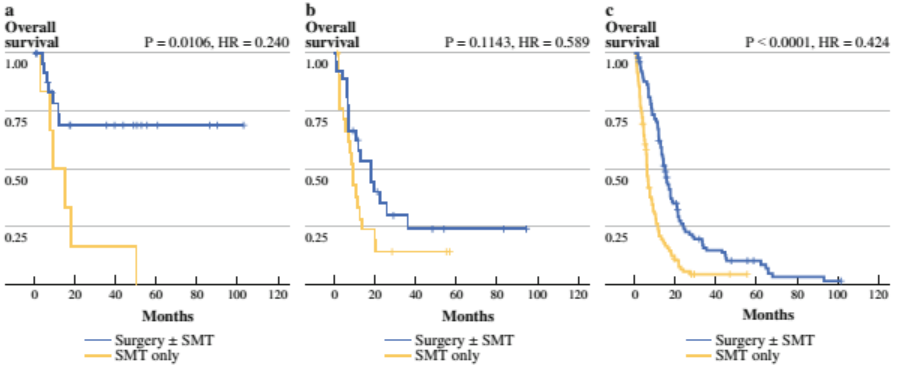


FIG. 3 **a** Overall survival for patients with M1a recurrence treated with surgery with or without SMT ($n = 26$, median survival NA, 4-year survival 69.3 %) vs. SMT alone ($n = 6$, median survival 12.4 months, 4-year survival 0 %). **b** Overall survival for patients with M1b recurrence treated with surgery with or without SMT ($n = 27$, median survival 17.9 months, 4-year survival 24.1 %) vs. SMT alone ($n = 22$, median survival 9.1 months, 4-year survival 14.3 %). **c** Overall survival for patients with M1c recurrence treated with surgery with or without SMT ($n = 108$, median survival 15.0 months, 4-year survival 10.5 %) vs. SMT alone ($n = 102$, median survival 6.3 months, 4-year survival 4.6 %)

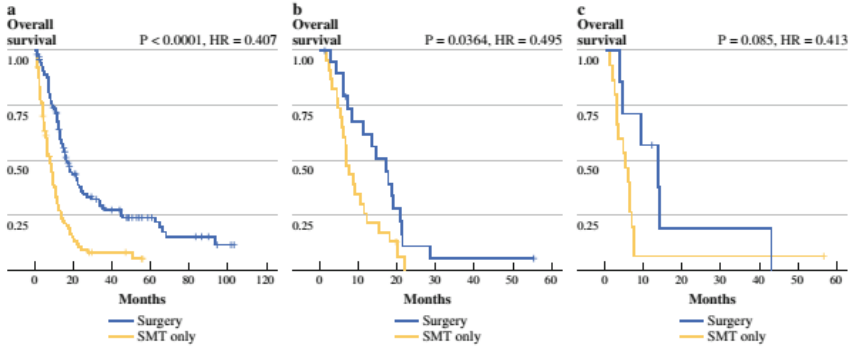


FIG. 4 **a** Overall survival for patients with stage IV recurrence of melanoma who had only one metastatic lesion treated by surgery ($n = 134$) or SMT only ($n = 92$). **b** Overall survival for patients with stage IV recurrence of melanoma who had 2 metastatic lesions treated by surgery ($n = 20$) or SMT only ($n = 23$). **c** Overall survival for patients with stage IV recurrence of melanoma who had 3 or more metastatic lesions treated by surgery ($n = 7$) or SMT only ($n = 15$)

Metastasectomy for Distant Metastatic Melanoma: Analysis of Data from the First Multicenter Selective Lymphadenectomy Trial (MSLT-I)

J. Harrison Howard, MD[1], John F. Thompson, MD[2], Nicola Mozzillo, MD[3], Omgo E. Nieweg, MD[4], Harald J. Hoekstra, MD[5], Daniel F. Roses, MD[6], Vernon K. Sondak, MD[7], Douglas S. Reintgen, MD[8], Mohammed Kashani-Sabet, MD[9], Constantine P. Karakousis, MD[10], Brendon J. Coventry, BM, BS, PhD[11], William G. Kraybill, MD[12], B. Mark Smithers, FRACS[13], Robert Elashoff, PhD[14], Stacey L. Stern, MS[1], Alistair J. Cochran, MD[15], Mark B. Faries, MD[1], and Donald L. Morton, MD[1]

SURGERY FOR DISTANT MELANOMA METASTASIS

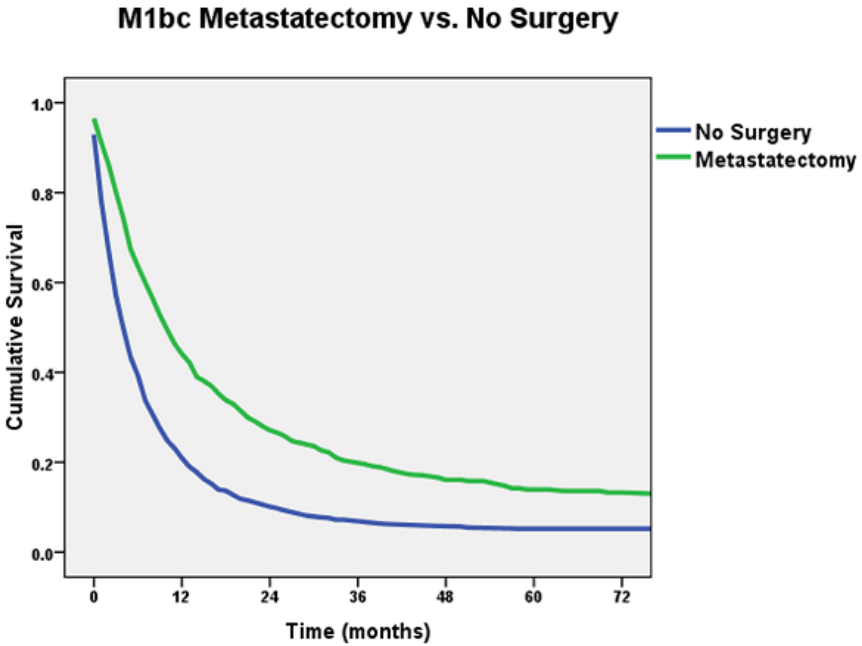
- Surgery in patients with metastatic disease in skin, soft-tissue, and lymph nodes; lungs; and gastrointestinal tract after complete metastasectomy

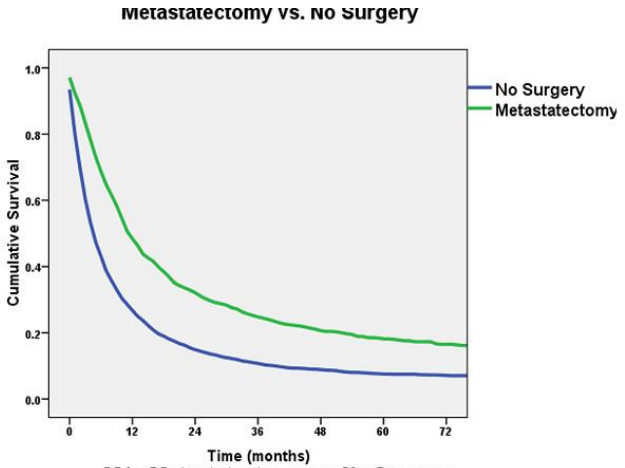
Author	Institution (Year)	Patients (n)	Median survival (mo.)	5-year OS (%)
Skin, soft-tissue and lymph node				
Eton *et al*	MDACC (1988)	57	10	5%
Barth *et al*	JWCI (1995)	281	15	14%
Pulmonary				
Petersen *et al*	Duke (2007)	249	19	21%
Andrews *et al*	Moffitt (2006)	86	35	33%
Leo *et al*	International Registry of Lung Metastases (2000)	282	19	22%
Tafra *et al*	JWCI (1995)	106	18	27%
Gastrointestinal, liver and adrenal				
Mittendorf *et al*	MDACC (2008)	20	20.7	Not Listed
Collinson *et al*	SMU (2008)	13	15	Not Listed
Rose *et al*	JWCI, SMU (2001)	18	18.2	23
Ollila *et al*	JWCI (1996)	46	48.9	41

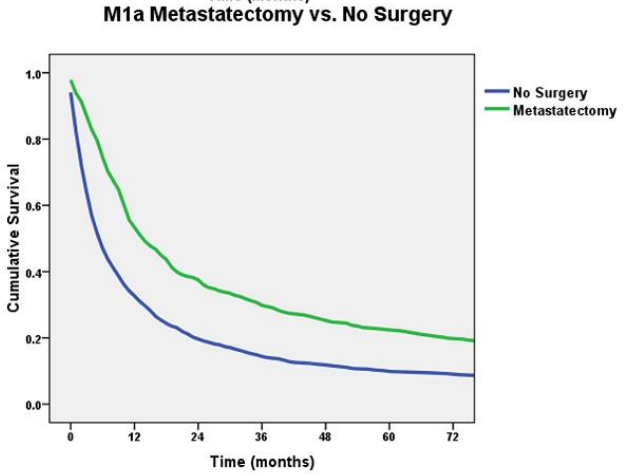
Leung AM, *et al.* Cancer J 2012;18(2):176-84

DOES METASTASECTOMY IMPROVE SURVIVAL IN PATIENTS WITH STAGE IV MELANOMA?

A cancer registry analysis of outcomes







Wasif N, *et al.* J Surg Oncol 2011: 104(2): 111-115. Reproduced with permission from John Wiley and Sons© 2011 Wiley-Liss, Inc..

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ESMO

SURGICAL MANAGEMENT OF MELANOMA LUNG METASTASIS

An analysis of survival outcomes in 292 consecutive patients

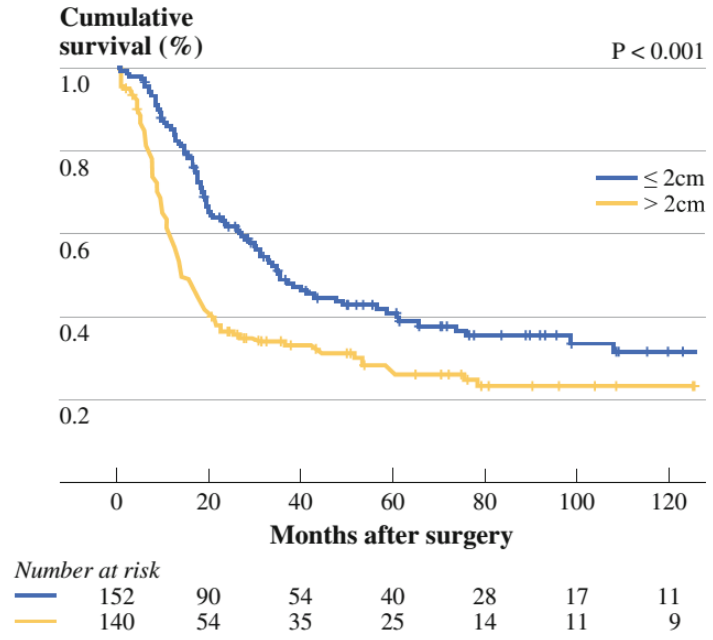


FIG. 2 Univariate analysis of lung metastasis size (≤2 cm *solid line*, >2 cm *dotted line*) and its influence on overall survival after surgery for MLM

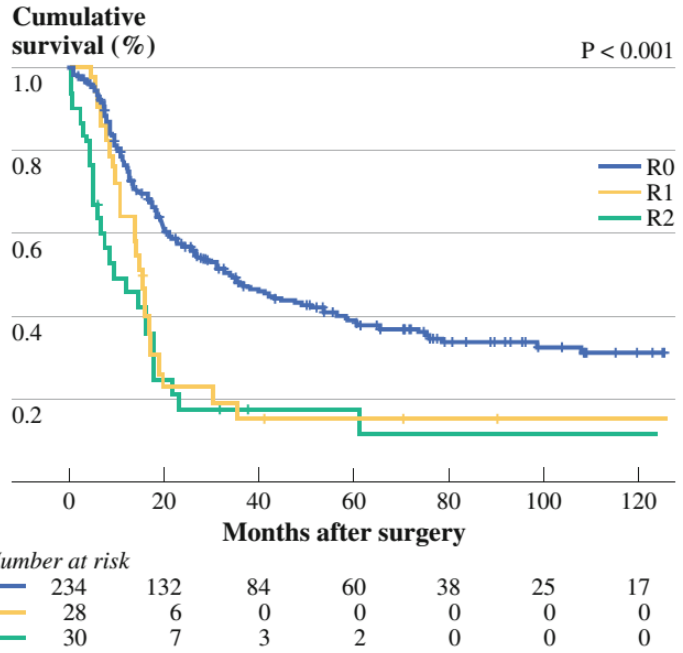


FIG. 3 Univariate analysis of surgical margin status (R0 *solid line*, R1 *dotted line*, R2 *broken line*) and its influence on overall survival after surgery for MLM

PET-CT

In the management of patients with stage IV and clinically evident stage III metastatic melanoma considered candidates for surgery: Evaluation of the additive value following conventional imaging

Results—PET-CT demonstrated unexpected melanoma metastases in 12 % of scans (4 out of 33). As a result the surgery was cancelled in two patients, and the planned approach was altered in another two patients to address the unexpected sites.. In 6 % of scans (2 out of 33) the unexpected metastases were detected in the extremities, not included in conventional imaging. Three scans (9%) showed false positive FDG avid findings which proved to be benign by subsequent stability or resolution with no therapy.

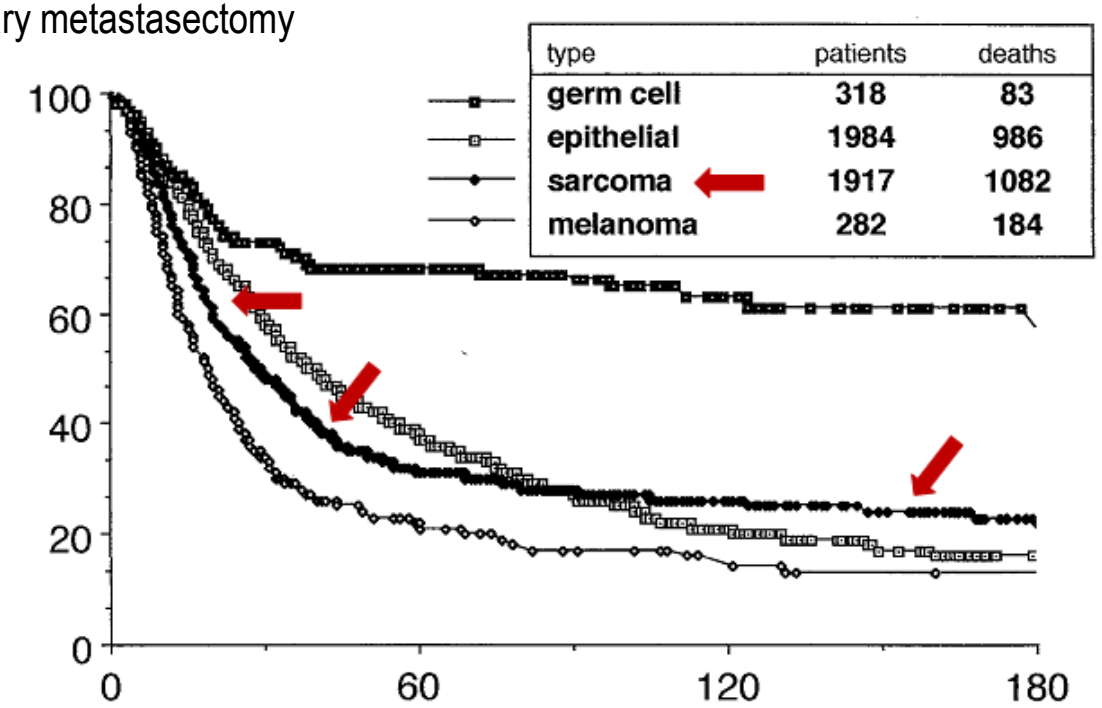
Conclusion—In patients with surgically-treatable metastatic melanoma, FDG PET-CT can detect unexpected metastases which are missed or not imaged with conventional imaging, and can be considered as part of preoperative workup.

Bronstein Y, *et al.* AJR Am J Roentgenol 2012: 198(4).

LONG-TERM RESULTS OF LUNG METASTASECTOMY

Prognostic analyses based on 5206 cases

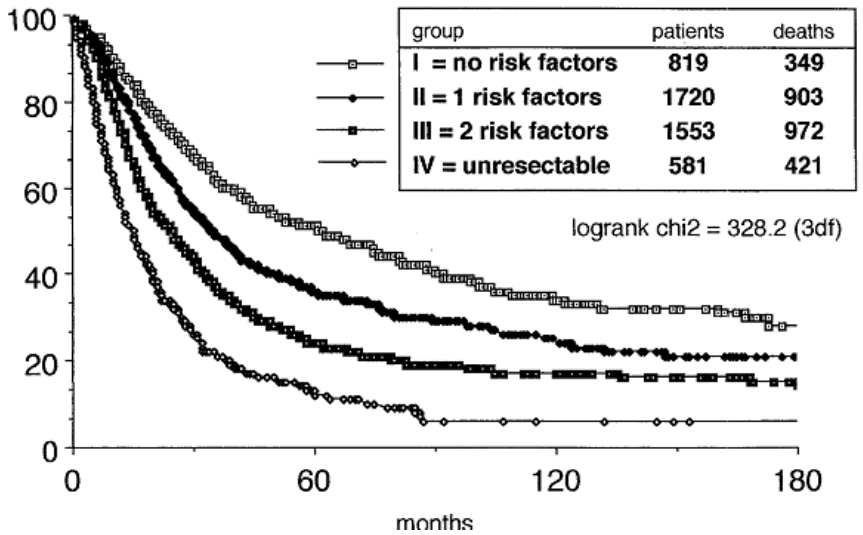
Objectives: The International Registry of Lung Metastases was established in 1991 to assess the long-term results of pulmonary metastasectomy

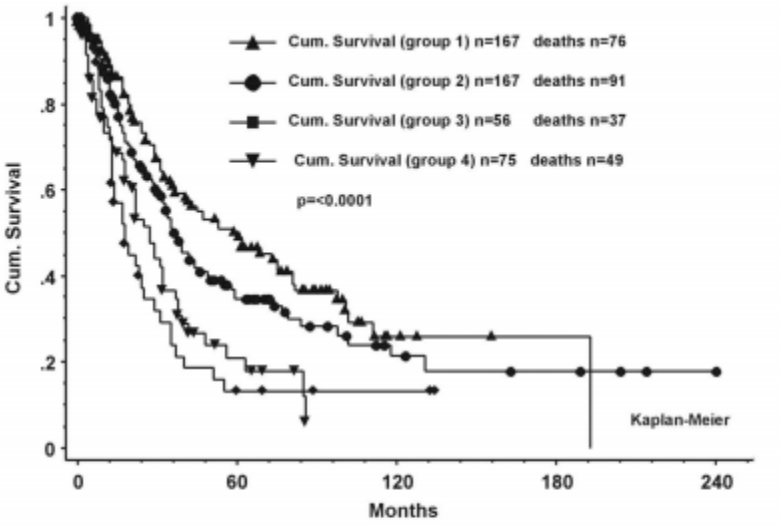


Reprinted from The Journal of Thoracic and Cardiovascular Surgery, 113(1), Pastorino U, *et al*. Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases, 37-49. Copyright 1997, with permission from Elsevier.

LONG-TERM RESULTS OF LUNG METASTASECTOMY

Prognostic analyses based on 5206 cases





Prognostic score after resection of lung metastases	
Metastases number	1 vs 2-3 vs >4
Time interval	<1 yr vs >1 yr vs >2 yr
Resection margin	R0, R1, R2

	5 - year surv.	5 - year at risk	10 - year surv.	10 - year at risk	15 - year surv.	15 - year at risk	median
Group 1 (no risk factor)	50%	47	26%	5	26%	1	59 m.
Group 2 (1 risk factor)	35%	31	21%	8	18%	4	36 m.
Group 3 (2 risk factors)	13%	4	13%	2			18 m.
Group 4 (incomplete res.)	18%	7					25 m.

1) Reprinted from The Journal of Thoracic and Cardiovascular Surgery, 113(1), Pastorino U, *et al.* Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases, 37-49, Copyright 1997, with permission from Elsevier. 2) Friedel G, *et al*. Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the international registry of lung metastases, European Journal of Cardio-Thoracic Surgery, 2002, 22(3): 335-344, by permission of Oxford University Press.

SYSTEMATIC REVIEW OF PULMONARY METASTASECTOMY FOR SARCOMA

- 1980 – 2006, n=1357
- N=1196: 1ry section, 43% re-resection
- Up to 10 thoracotomies
- 5 year survival: 34% for STS, 25% for bone
- Better survival for fewer mets and longer time interval
- Beats the expected survival for M1 sarcoma patients in the Thames Cancer Registry

- No randomised study
- Comparison: surgery for oligometastases *vs.* standard of care (chemotherapy) missing

Treasure T, *et al.* BMJ Open 2012: 2: e001736.

IS REPEAT PULMONARY METASTASECTOMY INDICATED FOR SOFT TISSUE SARCOMA?

Variable	Hazard Ratio (95% CI)	P-value
Age at diagnosis of primary tumour	0.90.67 (0.41 to 1.09)	0.033
Perioperative treatment at initial PM	8 (0.97 to 1.00)	0.10
Minimally invasive operation at initial PM	1.58 (1.02 to 2.45)	0.041
Disease-free interval[a]	1.02 (1.00 to 1.04)	0.009
No. of pulmonary nodules at recurrence	0.73 (0.63 to 0.83)	<0.001
Synchronous extrapulmonary disease at recurrence	0.13 (0.08 to 0.23)	<0.001
KPS scale at recurrence (%)	1.01 (0.99 to 1.06)	0.14

[a]From first PM to recurrence at any site per month

Chudgar NP, *et al.* Ann Thorac Surg 2017: 104: 1837-45.

SARCOMA TRIAL

Disease-specific survival for patients with pulmonary metastases, by treatment

	Treatment		
	No resection	Incomplete resection	Complete resection
Patients (n)	473	52	161
Median survival (months)	11	16	33*
3-year actuarial survival rate (%)	17	nr	46
*p<0.001 *vs.* No resection or Incomplete resection			

Billingsley KG, *et al.* Ann Surg 1999;5:602–12.

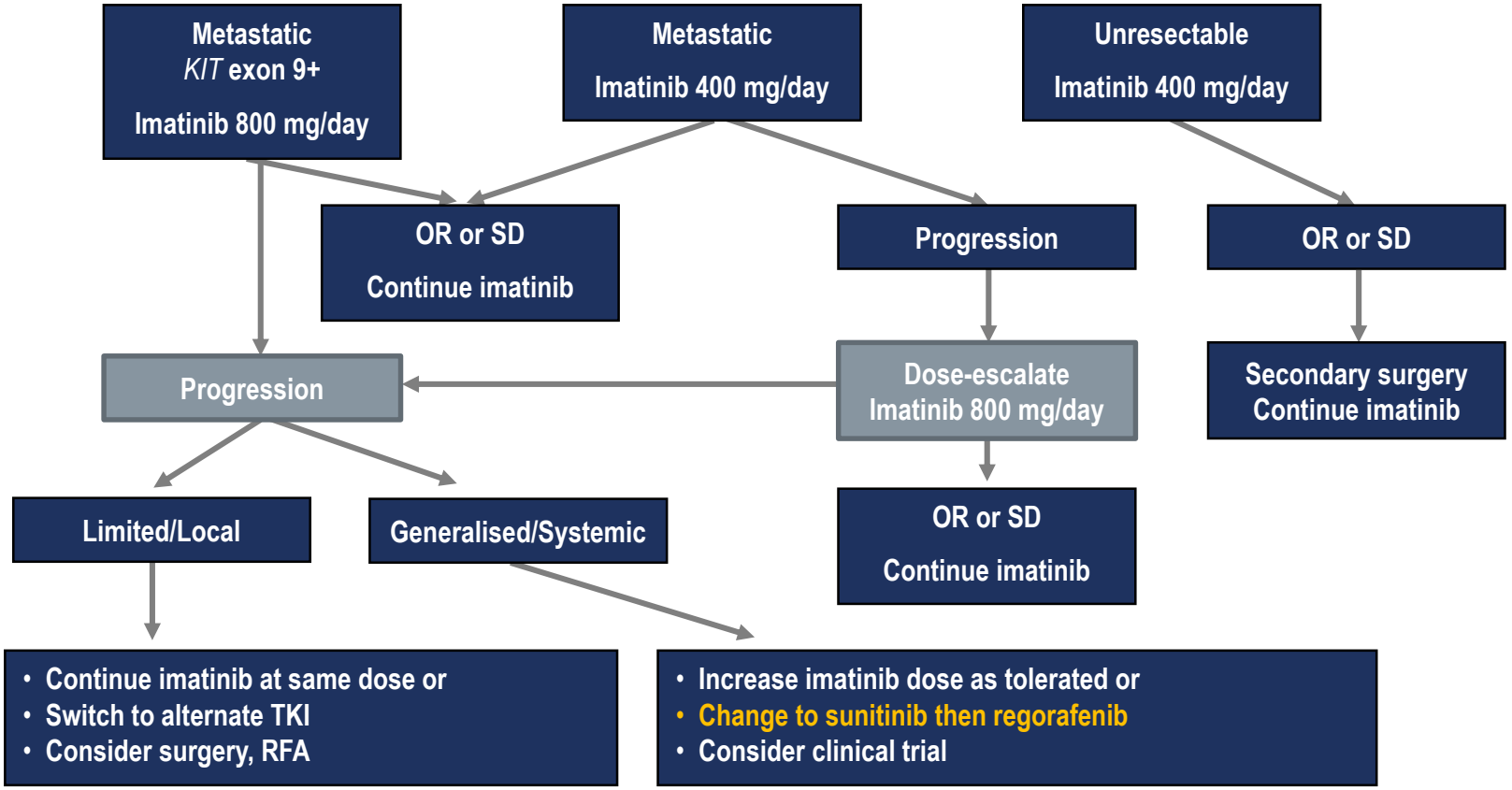
FIELDS FOR SURGERY DURING TKI THERAPY OF ADVANCED GISTS

- Removal of residual lesions, which have remained despite TKI therapy after previous response
- Resection of progressive disease whenever possible to beat resistance to TKI
- Treatment of emergency complications during TKI therapy (gastrointestinal bleeding, bowel obstruction, perforation)

SURGERY FOR RESIDUAL DISEASE - RATIONALE

- Dramatic efficacy of imatinib is time-limited
- Complete responses during therapy of TKI are rare
- In other advanced sarcomas metastasectomy is the only potentially curative treatment
- Common persistence of viable GIST cells after imatinib therapy – probability of developing resistant clones of GIST cells is proportional to the tumour mass

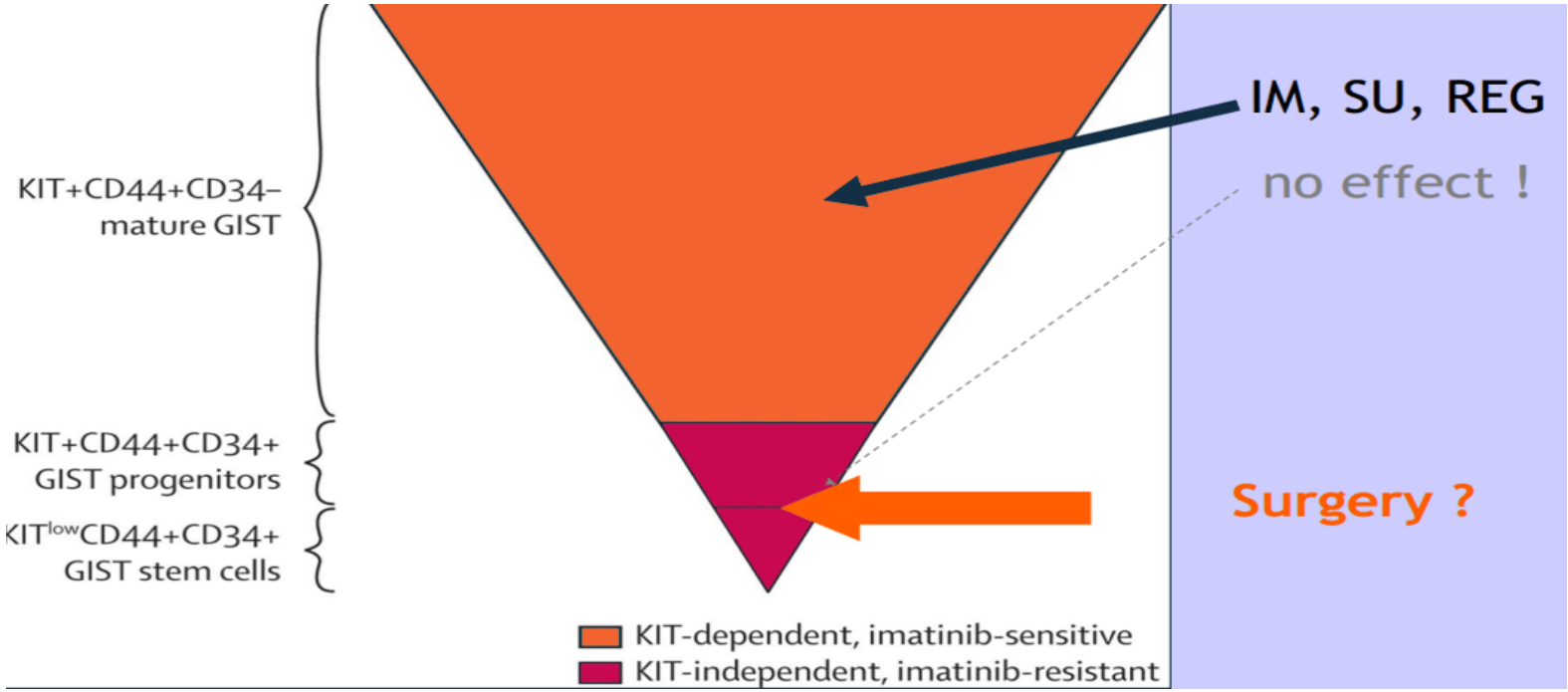
ALGORITHM: MANAGEMENT OF UNRESECTABLE OR METASTATIC GIST[1–3]



OR, overall response; RFA, radiofrequency ablation; SD, stable disease.

1. Reichardt P. EJC Suppl. 2006;4(suppl 1):19-26; 2. NCCN. Clinical Practice Guidelines. Soft tissue Sarcoma. V.2.2018; 3. Casali PG, *et al*. Ann Oncol. 2018;29 (suppl 4):iv68-iv78. ESMO-EUROCAN Clinical Practice Guidelines

WHICH PART OF THE TUMOUR DO WE ATTACK WITH DRUGS?



IM, imatinib; REG, regorafenib; SU, sunitinib

Bardsley M. Gastroenterology 2010;139:942–952; Heinrich M. Lancet Oncol 2010;11:910–911.

SURGERY AFTER TREATMENT WITH IMATINIB AND/OR SUNITINIB

In patients with metastasised gastrointestinal stromal tumours: Is it worthwhile?

Univariate analysis of tumour and treatment characteristics on progression-free and overall survival

	PFS Hazard ratio (95% CI)	P-value	OS Hazard ratio (95% CI)	P-value
Age at surgery		0.68		0.87
<60 years* (n=31)	1		1	
>60 years (n=24)	1.15 (0.58-2.29)		1.07 (0.47-2.43)	
Gender		0.19		0.68
Female* (n=20)	1		1	
Male (n=35)	0.63 (0.32-1.23)		0.68 (0.30–1.55)	
Response†		<0.05		<0.05
Yes* (n=35)	1		1	
No (n=20)	5.01 (2.46-10.22)		6.81 (2.83-16.38)	
Resection		<0.05		0-06
Complete* (n=29)	1		1	
Incomplete (n=26)	2.44 (1.20-4.96)		2.28 (0.98-5.28)	
Adjuvant therapy		0.81		0.69
Yes* (n=46)	1		1	
No (n=9)	0.89 (0.34-2.31)		1.28 (0.38-4.32)	
Location metastasis‡		0.52		0.57
Abdominal* (n=33)	1		1	
Liver (n=22)	0.79 (0.45-1.40)		1.21 (0.63-2.30)	

*Reference group; †response on systemic therapy; ‡patients with both liver and abdominal metastasis were grouped together in the abdominal group; ‖ surgery before start of systemic therapy. CI, confidence interval; OS, overall survival; PFS, progression –free survival. .

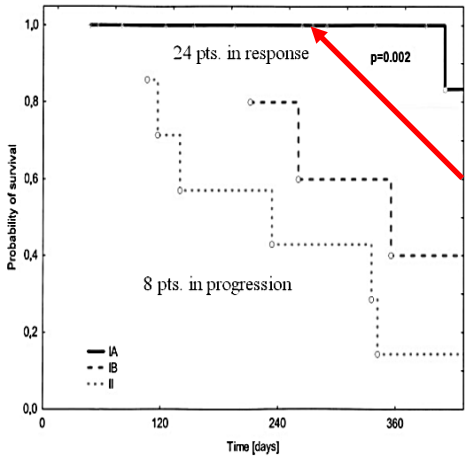
Tielen R, *et al.* World J Surg Oncol 2010;11:910–911.

RESPONDING PATIENTS AFTER SURGERY OF RESIDUAL DISEASE HAVE DURABLE (PROLONGED?) COMPLETE REMISSIONS

Surgical Treatment of Patients With Initially Inoperable and/or Metastatic Gastrointestinal Stromal Tumors (GIST) During Therapy With Imatinib Mesylate

Journal of Surgical Oncology 2006;93:304–311

PIOTR RUTKOWSKI, MD, PhD,[1]* ZBIGNIEW NOWECKI,[1] PAWEL NYCKOWSKI,[2] WIRGINIUSZ DZIEWIRSKI,[1] URSZULA GRZESIAKOWSKA,[3] ANNA NASIEROWSKA-GUTTMEJER,[4] MAREK KRAWCZYK,[2] AND WLODZIMIERZ RUKA[1]

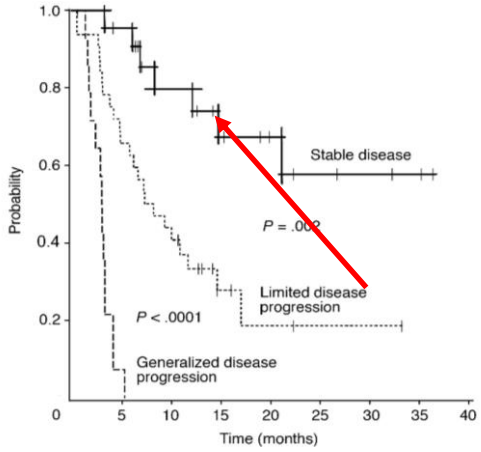


VOLUME 24 · NUMBER 15 · MAY 20 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Surgical Management of Advanced Gastrointestinal Stromal Tumors After Treatment With Targeted Systemic Therapy Using Kinase Inhibitors

Chandrajit P. Raut, Matthew Posner, Jayesh Desai, Jeffrey A. Morgan, Suzanne George, David Zahrieh, Christopher D.M. Fletcher, George D. Demetri, and Monica M. Bertagnolli

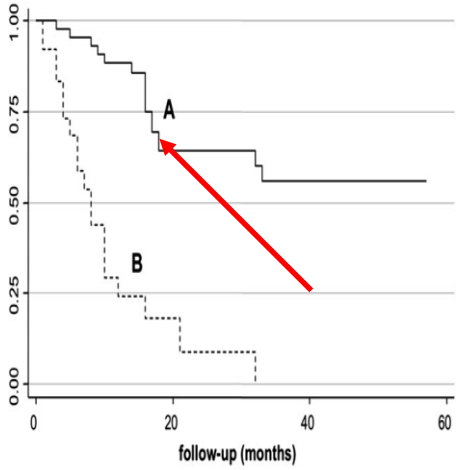


original article

Annals of Oncology 21: 403–408, 2010
doi: 10.1093/annonc/mdp310
Published online 23 July 2009

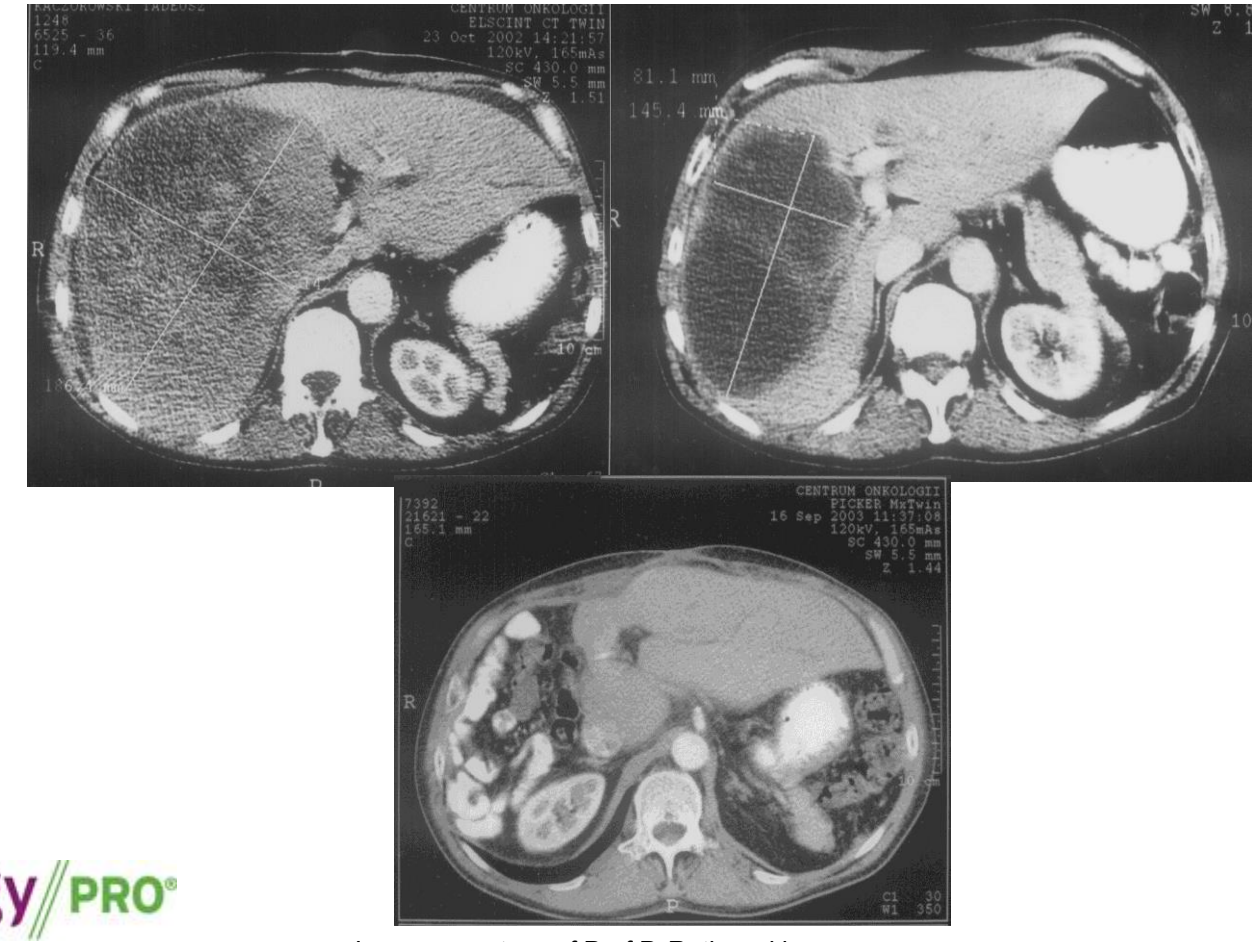
Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients?

C. Mussi[1†], U. Ronellenfitsch[2†], J. Jakob[2], E. Tamborini[3], P. Reichardt[4], P. G. Casali[5], M. Fiore[1], P. Hohenberger[2] & A. Gronchi[1*]



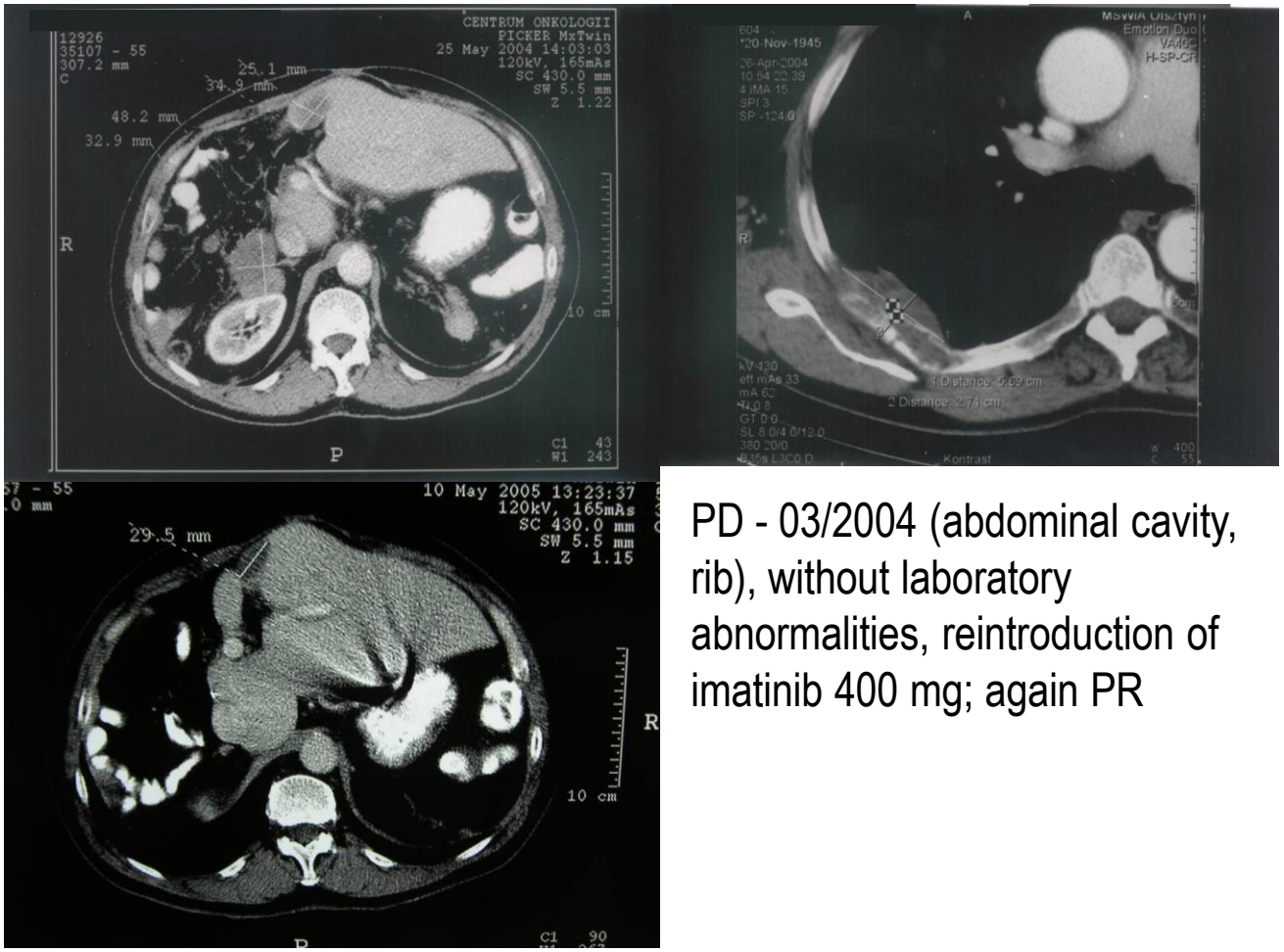
1.Rutkowski P, *et al.* J Surg Oncol 2006;93:304–311; 2. Raut CP, *et al.* J Clin Oncol, 24(15), 2006: 2325-31. Reprinted with permission. © 2006 American Society of Clinical Oncology. All rights reserved; 3. Mussi C, et al. Ann Oncol 2010;21:403–8, by permission of Oxford University Press on behalf of the European Society for Medical Oncology;
See also DeMatteo RP, et al. Ann Surg 2007;245;347–52; Gronchi A, Ann Surg 2007;245:341–6

RE-SECTION OF RESPONDING OLIGOMETASTATIC GIST TO THE LIVER AFTER RESPONSE TO IMATINIB THERAPY



Images courtesy of Prof P. Rutkowski

DO NOT STOP IMATINIB AFTER RESECTION OF RESIDUAL DISEASE

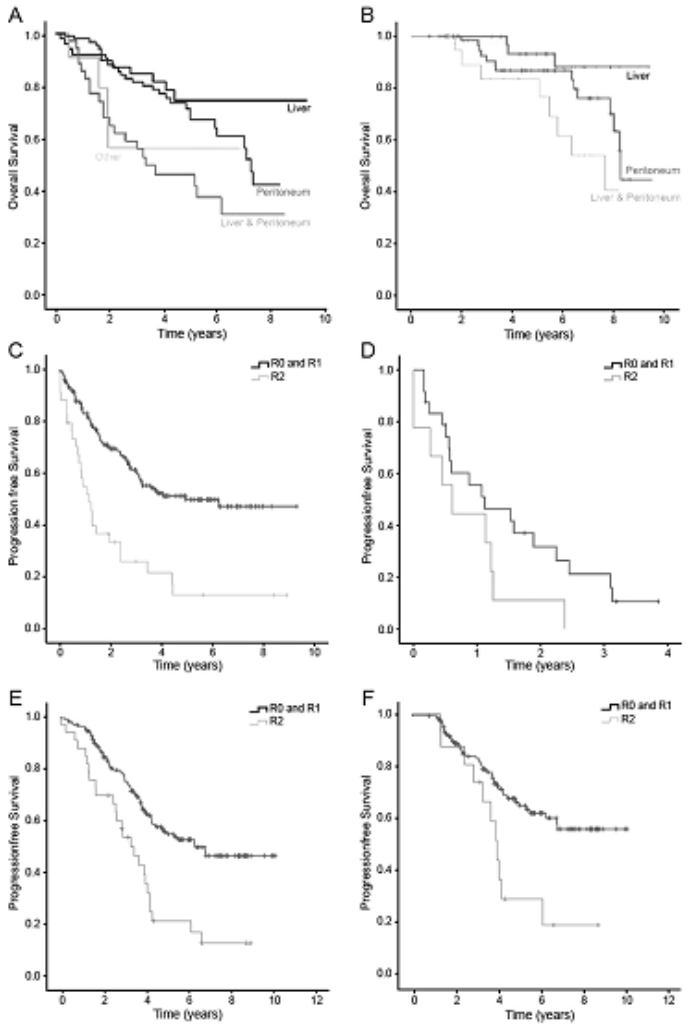


PD - 03/2004 (abdominal cavity, rib), without laboratory abnormalities, reintroduction of imatinib 400 mg; again PR

Images courtesy of Prof P. Rutkowski

LONG-TERM FOLLOW-UP OF PATIENTS WITH GIST

Undergoing metastasectomy in the era of imatinib – Analysis of prognostic factors (EORTC-STBSG collaborative study)



Overall survival curves for patients who understand metastasectomy depending on affected organ system in the complete population (2A) and restricted to non-progressive patients (2B). Time-to progression curves calculated from date of surgery until progression for non-progressing GIST (2C) and progressing GIST at the time of surgery (2D). Time to progression curves calculated from date of first imatinib for metastatic disease until progression or death in all patients (2E) and restricted to non-progressing patients only (2F).

Reprinted from European Journal of Surgical Oncology, 40(4), Bauer S, *et al.* Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib – Analysis of prognostic factors (EORTC-STBSG collaborative study), 412-419. Copyright 2014, with permission from Elsevier

LONG-TERM FOLLOW-UP OF PATIENTS WITH GIST

Undergoing metastasectomy in the era of imatinib – Analysis of prognostic factors (EORTC-STBSG collaborative study)

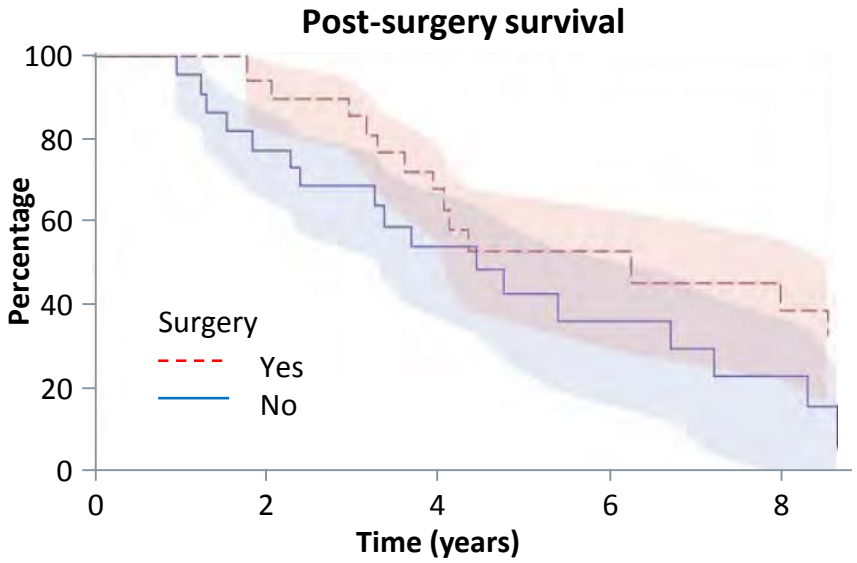
Survival after start of imatinib for M1

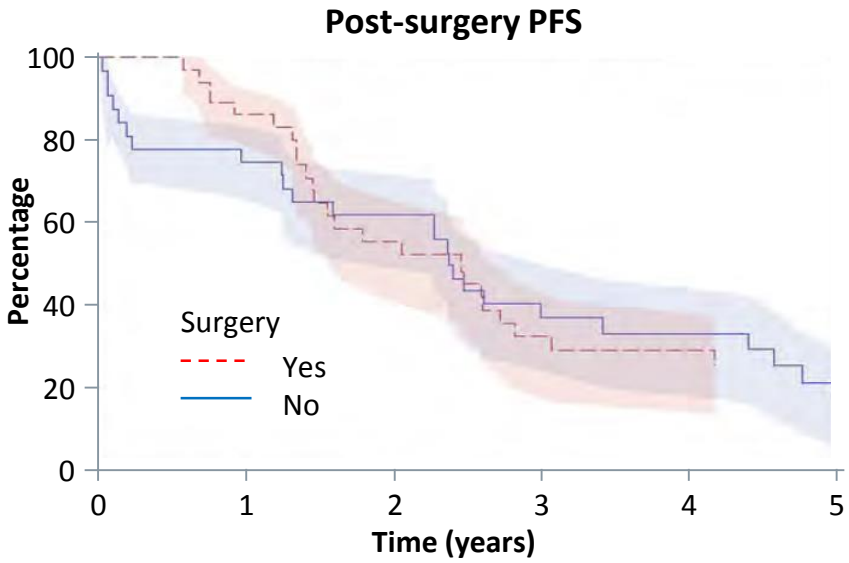
Indication/Condition	Result	p
R0/R1 resection	Median OS: 8.7 years	
R2 resection	Median OS: 5.3 years	0.0001
Resected in remission:		
R0/R1 resection	Median not reached	
R2 resection	Median OS: 5.1 years	0.0001
R0/R1 resection	**TTRec**: median not reached	
R2 resection	Median TTRec: 1.9. years	0.0001

Bauer S, *et al.* Eur J Surg Oncol 2014; 40(4):412-419.

SURGICAL RESECTION OF METASTATIC GIST

- Results of a cross-match comparison on the EORTC Intergroup Study 62005, aimed at assessing the clinical activity of imatinib at two dose levels in patients with unresectable or metastatic GIST

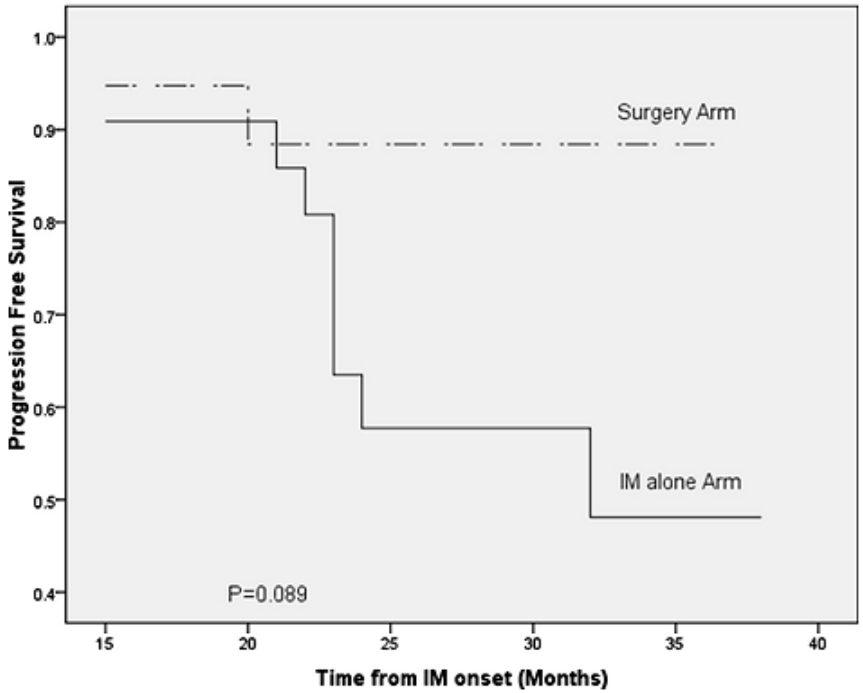


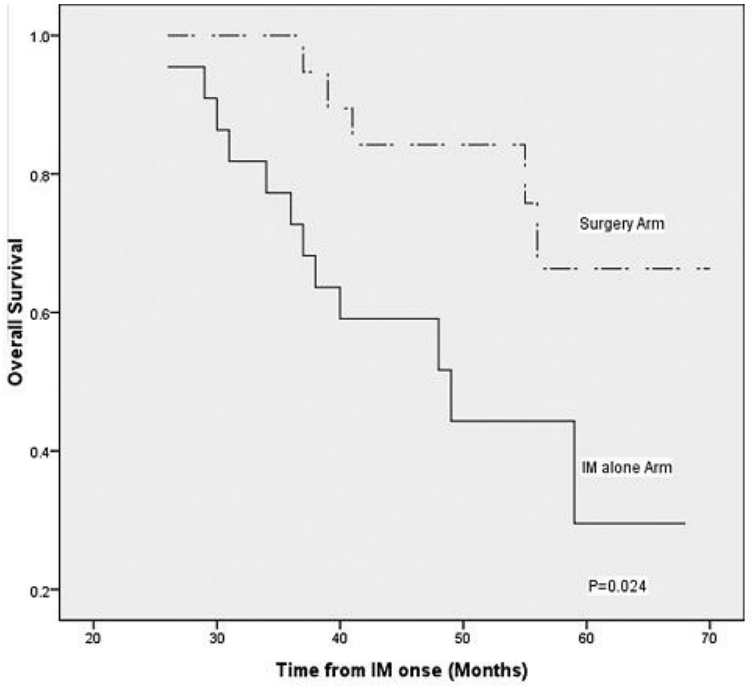


Hohenberger P, *et al.* CTOS 2014 (Paper 007).

IS THERE A ROLE OF SURGERY…

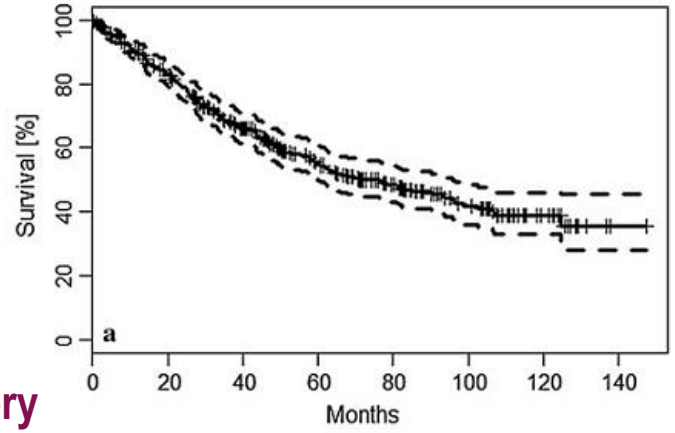
…In patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: A prospective randomised trial in China



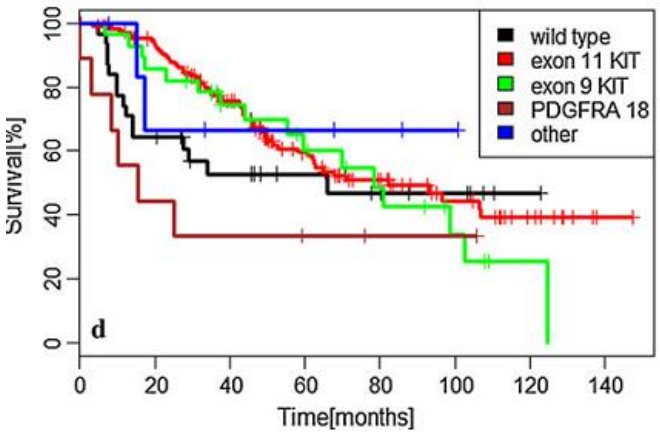


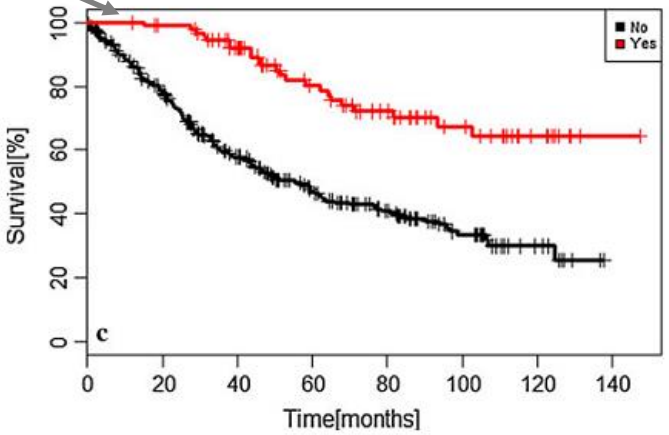
WHAT ARE THE CURRENT OUTCOMES OF ADVANCED GASTROINTESTINAL STROMAL TUMOURS

Who are the long-term survivors treated initially with imatinib?

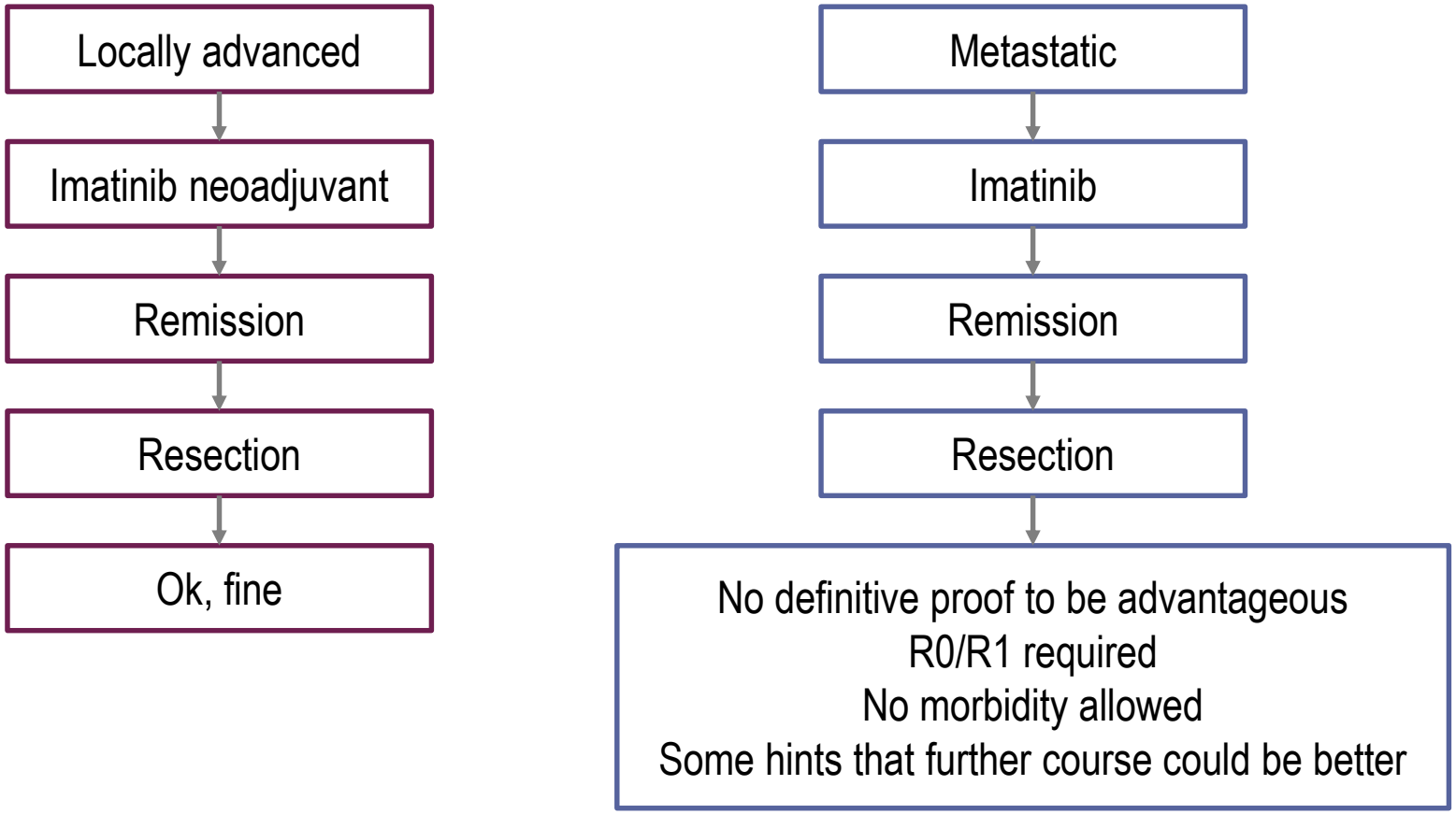


Impact of surgery





GIST TUMOURS



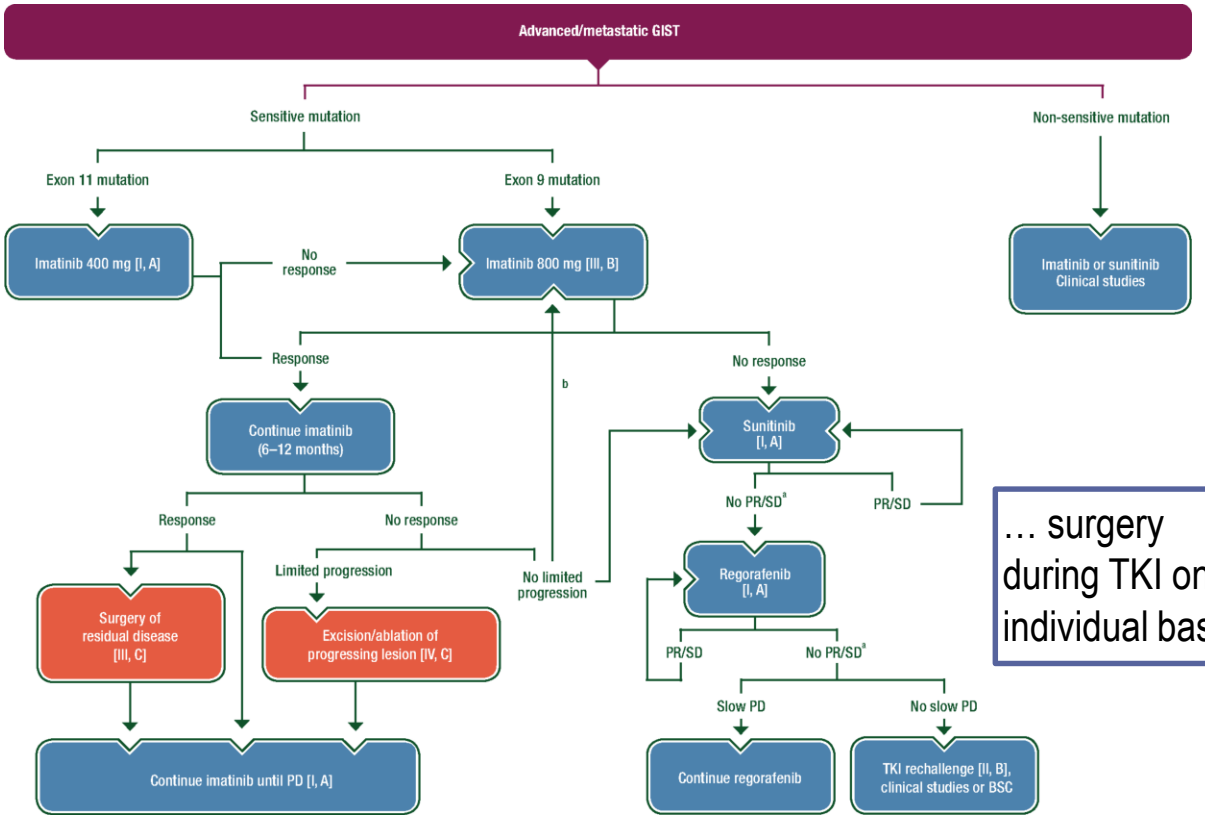
GASTROINTESTINAL STROMAL TUMOURS

ESMO clinical recommendations for diagnosis, treatment and follow-up

Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up

P. G. Casali, N. Abecassis, H. T. Aro, S. Bauer, R. Biagini, S. Bielack, S. Bonvalot, I. Boukovinas, J. V. M. G. Bovee, T. Brodowicz, J. M. Broto, A. Buonadonna, E. De Álava, A. P. Dei Tos, X. G. Del Muro, P. Dileo, M. Eriksson, A. Fedenko, V. Ferraresi, A. Ferrari, S. Ferrari, A. M. Frezza, S. Gasperoni, H. Gelderblom, T. Gil, G. Grignani, A. Gronchi, R. L. Haas, B. Hassan, P. Hohenberger, R. Issels, H. Joensuu, R. L. Jones, I. Judson, P. Jutte, S. Kaal, B. Kasper, K. Kopeckova, D. A. Krákorová, A. Le Cesne, I. Lugowska, O. Merimsky, M. Montemurro, M. A. Pantaleo, R. Piana, P. Picci, S. Piperno-Neumann, A. L. Pousa, P. Reichardt, M. H. Robinson, P. Rutkowski, A. A. Safwat, P. Schöffski, S. Sleijfer, S. Stacchiotti, K. Sundby Hall, M. Unk, F. Van Coevorden, W.T.A. van der Graaf, J. Whelan, E. Wardelmann, O. Zaikova & J. Y. Blay, on behalf of the ESMO Guidelines Committee and EURACAN

Management of advanced/metastatic GIST



… surgery during TKI on individual basis

[a]Surgery of limited progression may be considered
[b]If previously treated with 400 mg imatinib

BSC, best supportive care; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor

Casali FG, *et al.* Ann Oncol 2018;29(Supplement_4):iv68-iv78, doi:10.1093/annonc/mdy095. by permission of Oxford University Press on behalf of the European Society for Medical Oncology.

INTERGROUP STUDY (EORTC 62063)

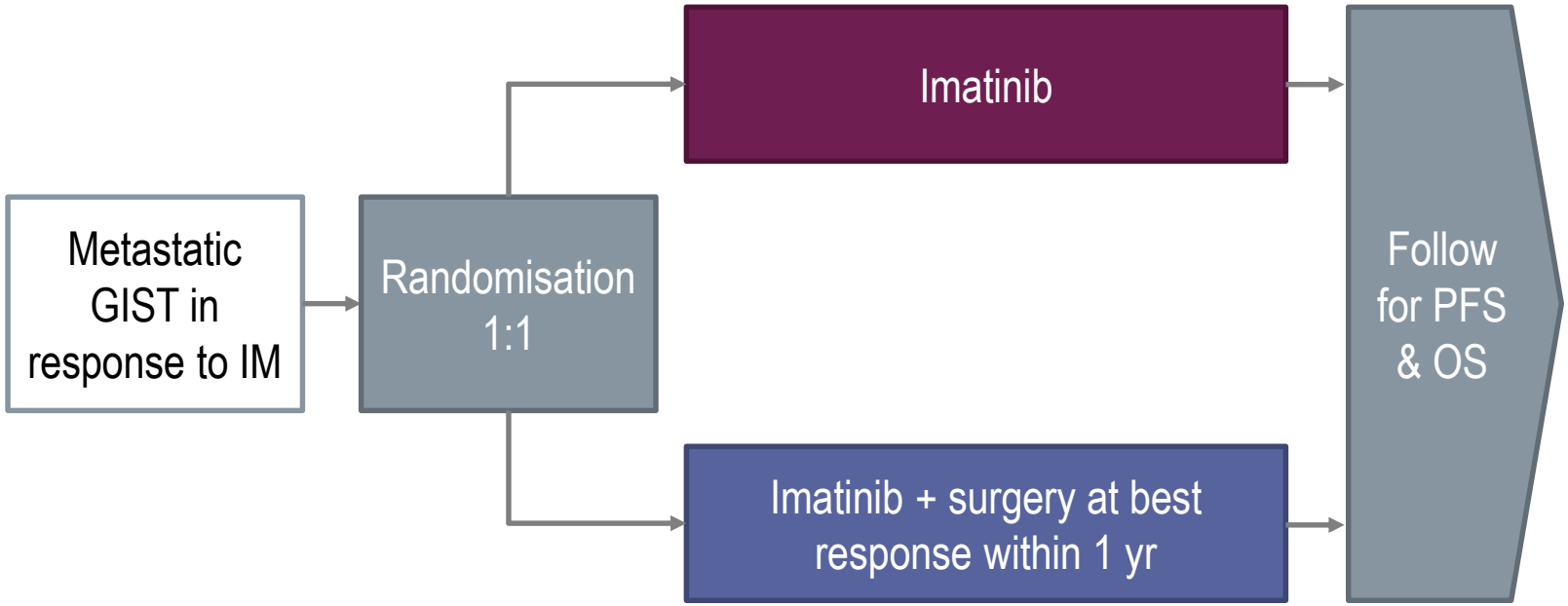
A phase III randomised study evaluating surgery of residual disease in patients with metastatic gastro-intestinal stromal tumour responding to imatinib mesylate

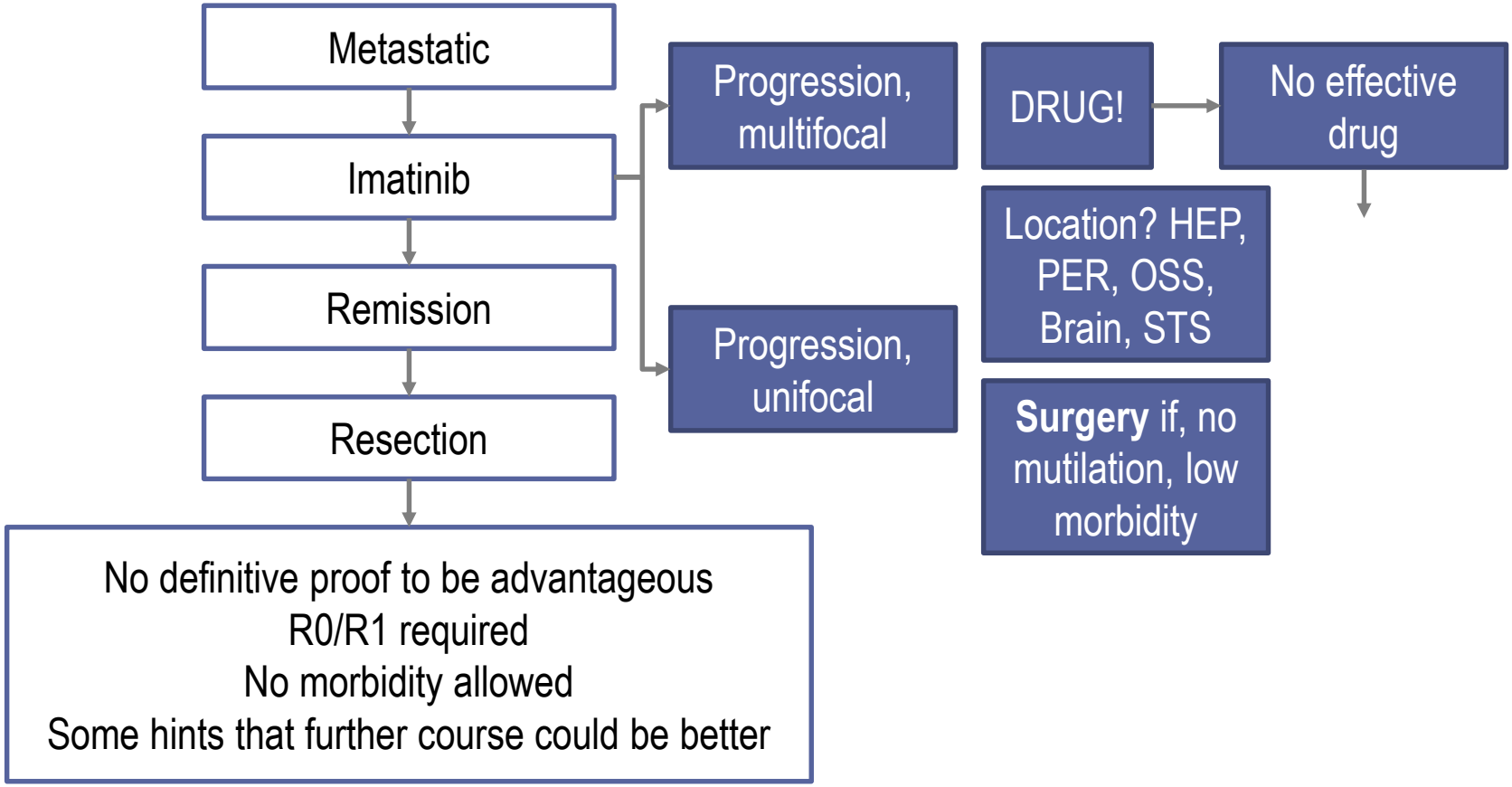
- Open-label
- Randomisation 1:1
- 2 arms: Imatinib *vs.* imatinib + surgery
- 350 patients
- 59 sites (Europe and Australia)

Collaborative groups: EORTC Soft Tissue and Bone Sarcoma Group (EORTC STBSG), Italian Sarcoma Group (ISG), French Sarcoma Group (FSG) – All French Centers participating through the FNCLCC, Australian Gastro-Intestinal Trials Group (AGITG)

STOPPED DUE TO POOR ACCRUAL

Study Design





SEVERAL PUBLISHED STUDIES IN GIST

Conclusions:

- Maintenance of imatinib therapy after surgery is crucial;
- R0/R1 surgery
- Final impact on survival and time of implementation of surgery is controversial;
- Bias of this study? Super-selection of the cases?

KEY CONCLUSIONS

- Patients suffering from an oligometastatic or oligo-recurrent disease, have a certain potential for a curative approach by local treatment measures
- Precise staging is crucial (PET/CT; CT)
- Surgery and radiotherapy remain the two main treatment approaches to gain a high local tumour control rate
- Level of evidence: in majority of tumours no randomised study - Comparison: surgery for oligometastases *vs*. standard of care (chemotherapy) missing
- This is also the case of a metastasised disease with a limited number of metastases in the lungs or at other sites

KEY CONCLUSIONS

- R0 resection/complete tumour destruction is a must, there is no room for debulking
- This is not removal of residual tumour after preoperative chemotherapy of widespread disease
- These highly selected and sometimes sophisticated measures should be agreed upon in an interdisciplinary tumour board in expert centre
- Shared decision-making with the patient is mandatory as the (slim and often transient) chance of disease relief must be weighed against the risks of the treatment

THANK YOU!

December 2018

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DISCLOSURES

Piotr Rutkowski has reported honoraria received for speaker, consultancy or advisory role from:

MSD, BMS, Novartis, Roche, Blueprint Medicines, Eli Lilly, Amgen, Pfizer, Pierre Fabre, Bayer

PI for Novartis, BMS, Roche, Janssen, MSD, Amgen. Honoraria received for speaker role from Educational Providers:

Center for Postgraduate Education, Poland; ViaMedica, Poland. Institutional financial support to clinical studies from Pharma to his Department at Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland: Novartis, BMS, Roche.

Ahmad Awada has reported Advisory Board honoraria, lectures fees and consultation fees from: Roche, Lilly, Eisai, Pfizer, Novartis, MSD and BMS.

Peter Hohenberger has reported no conflict of interest