

Management of Peritoneal Surface Malignancy

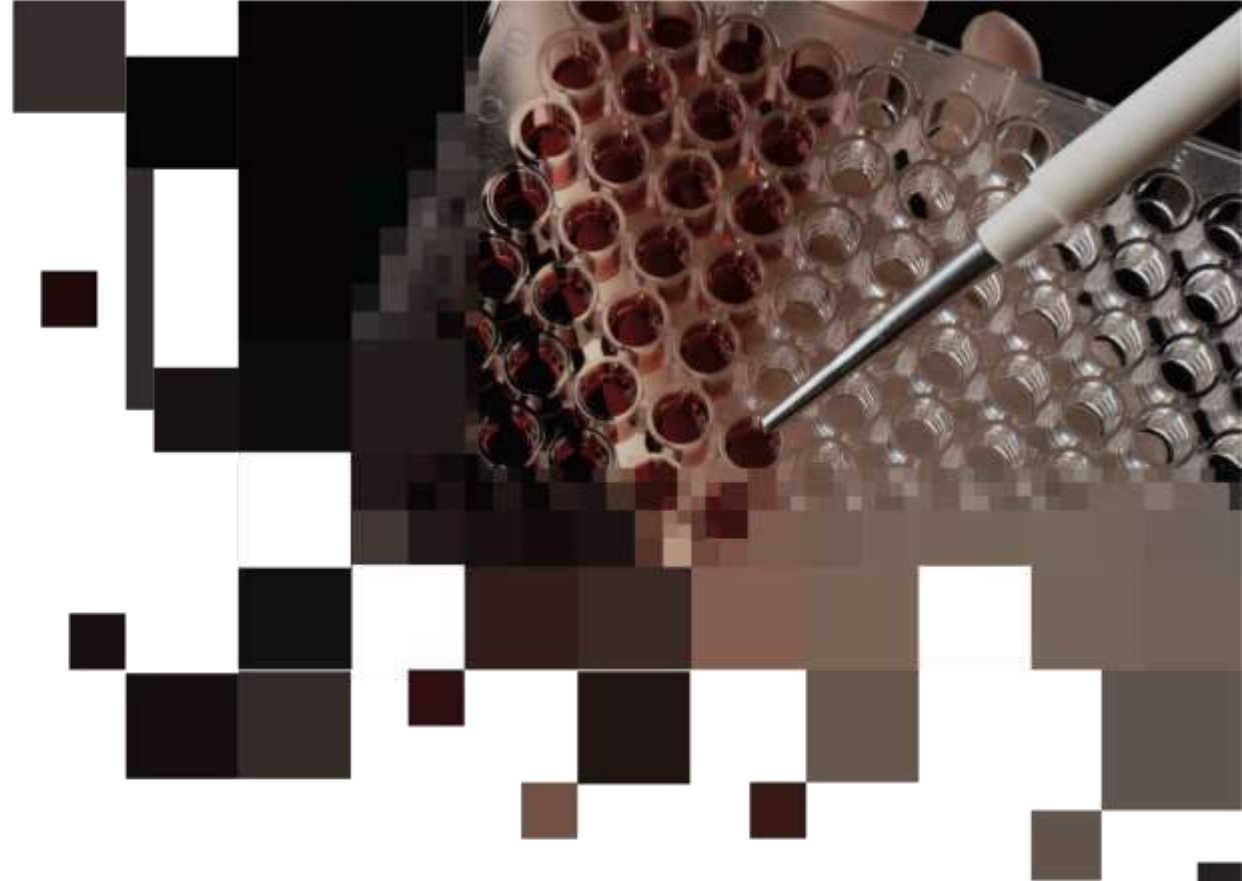


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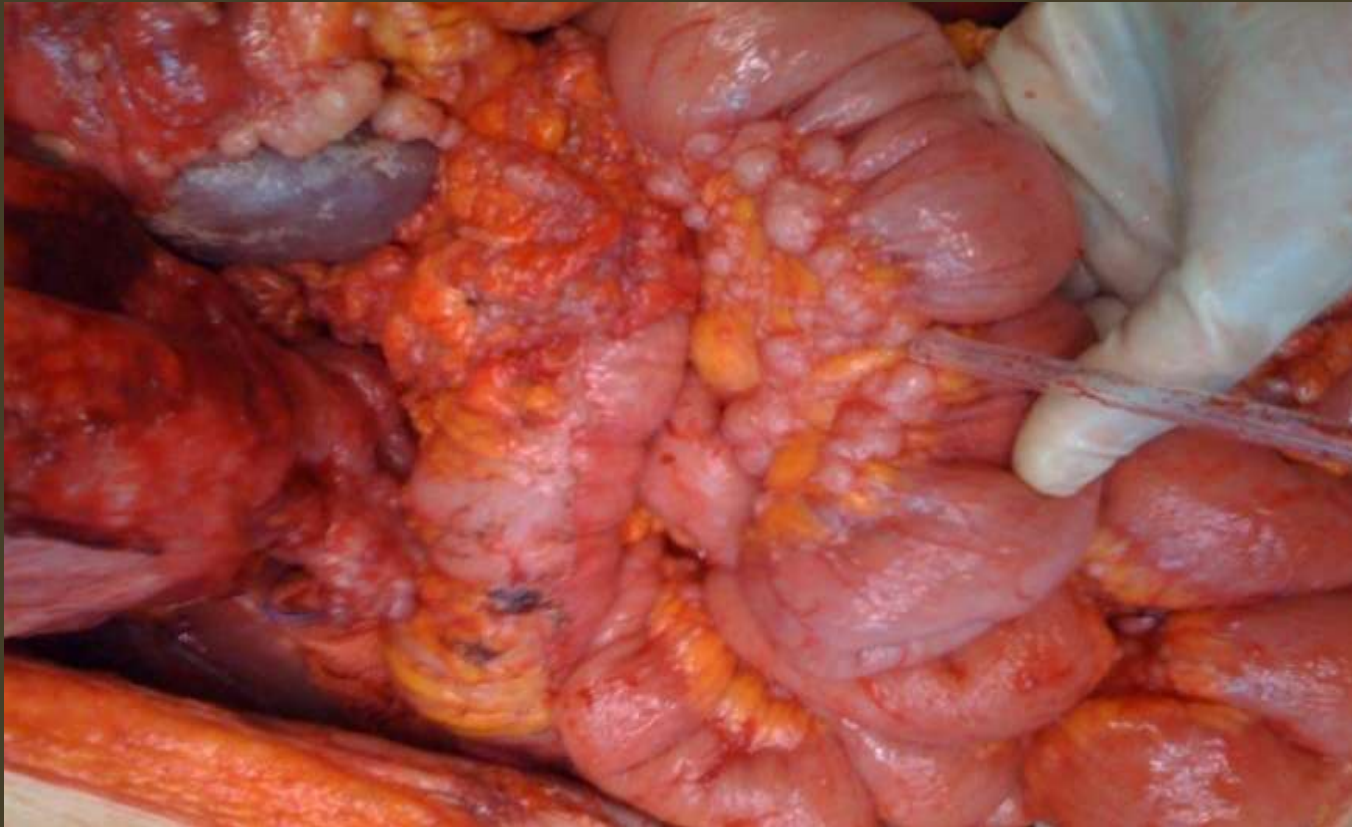
HIPEC for Peritoneal Mesothelioma

K. Van der Speeten, MD, PhD
Irkutsk, 10/08/17



- Background & History
- Pathology
- Diagnosis & Staging
- Clinical Results of CRS& HIPEC

Background & History



Background & History

- Rare cancer arising from the peritoneal lining of the abdominal cavity
- 1-3/mil/year
- 7-10 % of all mesotheliomas
- Median age at diagnosis : 50 yrs
- Male/female = 1 (<> pleural mesothelioma)
- Correlated with exposure to mineral erionite, asbestos and simian virus 40

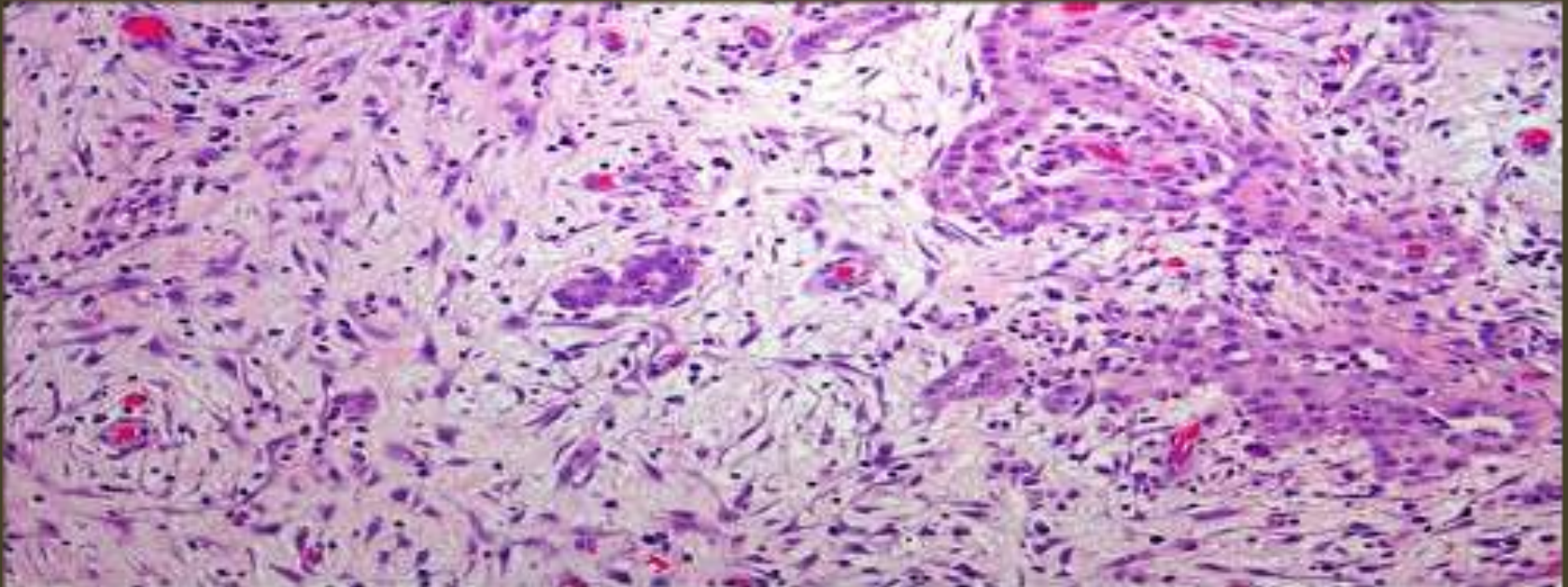


Background & History

Table 1.1. Important historical events between 1767 and 1972

Year	Researcher	Event
1767	Lietaud	Report of first possible case of pleural mesothelioma
1854	von Rokitansky	First pathologic description of peritoneal mesothelioma
1870	Wagner	First pathologic description of pleural mesothelioma
1890	Biggs	First American case
1920	Du Bray, Rosson	First use of the term <i>mesothelioma</i>
1924	Robertson	Best review of literature up to that time
1942	Stout, Murray	Further evidence on histogenesis
1953	Weiss	Association with pleural mesothelioma made in Germany
1954	Leichner	Association of asbestosis with peritoneal mesothelioma
1957	Godwin	Clear pathologic criteria for pleural mesothelioma
1960	Winslow, Taylor	Clear pathologic criteria for peritoneal mesothelioma
1960	Wagner	Mesothelioma associated with northwest Cape crocidolite
1964	Enticknap, Smither	Association of asbestos and peritoneal mesothelioma
1965	Selikoff	New York Academy of Science Symposium, report on U.S. insulators
1969	Wagner	Animal model further perfected
1972	Stanton, Wrench	Stanton hypothesis on the importance of fiber size/length

Pathology



Pathology

MESOTHELIOMA : a 'spectrum' - disease

Classification of peritoneal mesotheliomas

Benign

- Adenomatoid mesothelioma

- Localized fibrous mesothelioma

Borderline

- Multicystic peritoneal mesothelioma

- Well-differentiated papillary mesothelioma of peritoneum

Malignant

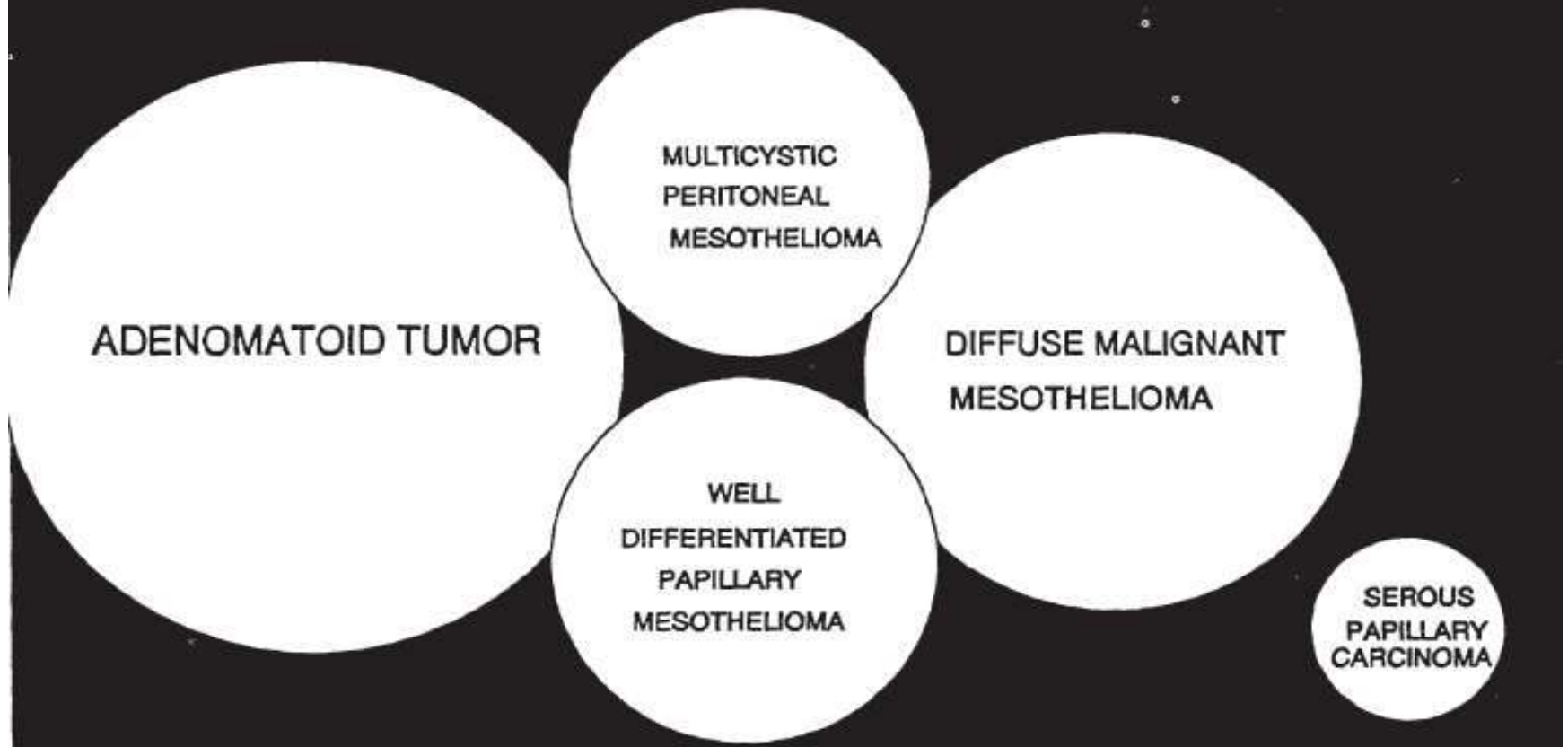
- Epithelial mesothelioma

- Fibrosarcomatous mesothelioma

- Mixed-type mesothelioma

Pathology

BIOLOGICAL AGGRESSIVENESS OF PERITONEAL MESOTHELIAL LESIONS



Pathology

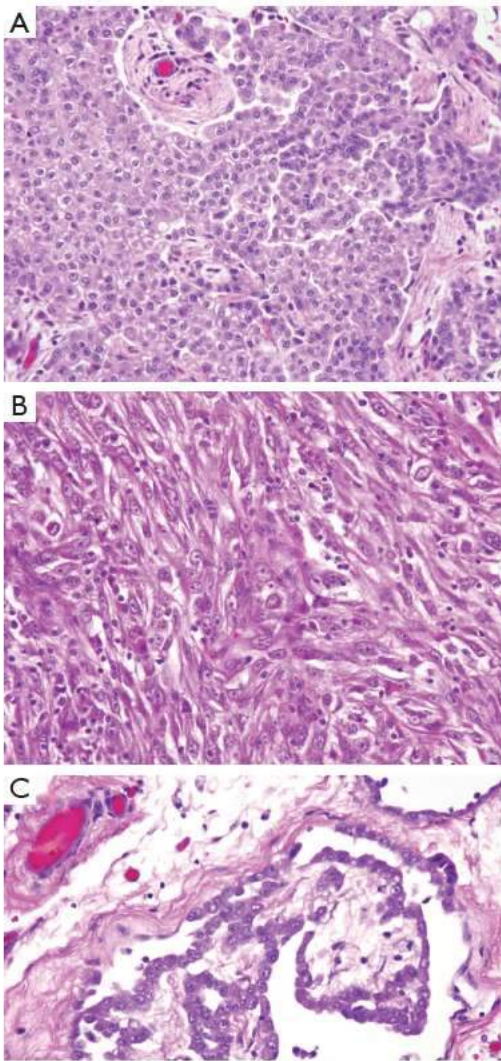


Figure 3 Histopathology (100×) showing tubulo-papillary (A), epithelioid (B), and sarcomatoid (C) mesothelioma.

Pathology

Table 7. Peritoneal Malignant Mesothelioma (PMM) Versus Papillary Serous Carcinoma (PSC) and Nongynecologic Adenocarcinoma (AdCa)

Marker	Current Value/Comments
Positive mesothelioma markers	
Calretinin	Useful. Positive in 85%–100% of PMM cases, but reactivity in 0%–38% PSC limits its use as a single marker.
D2-40	Potentially useful. Positive in 93%–96% of PMM cases, but wide spectrum of positivity in PSC from 13% to 65%; requires more data in this context.
CK5/6	Not useful. Positive in 53%–100% of PMM cases, but positive in 22%–35% of PSC cases.
WT-1	Not useful. Positive in 43%–93% of PMM, but 89%–93% of PSC are positive.
PSC markers	
MOC-31	Very useful. Positive in 5% of PMM and 98% of PSC.
BG8	Very useful. Positive in 3%–9% of PMM and 73% of PSC.
Ber-EP4	Useful. Positive in 9%–13% of PMM and 83%–100% of PSC.
B72.3	Limited utility. Positive in 0%–3% of PMM versus 65%–100% of PSC, but many trace/focal.
CEA	Not useful. Zero percent PMM but 0%–45% of PSC (mean, 20%), sensitivity in PSC is too low compared with other choices.
Estrogen receptor	Useful. Sixty percent to 93% in PSC, and negative or very low positive rate (0%–8%) in PMM.
Progesterone receptor	Limited utility. Lower sensitivity than estrogen receptor, but uniformly negative in PMM. May be valuable if positive.
PMM versus nongynecologic AdCa (biliary, pancreatic, gastric)	
Calretinin	Very useful. Positive in 85%–100% of PMM but also positive in 10% of pancreatic AdCa, so limited as a single marker.
WT-1	Very useful. Positive in 43%–93% of PMM, 3% of gastric AdCa, negative in pancreatic AdCa.
D2-40	Potentially useful. Positive in 93%–96% of PMM, negative in pancreatic and gastric AdCa (but limited data).
CK5/6	Not useful. Positive in 53%–100% of PMM, but 38% pancreatic AdCa positive.
MOC-31	Very useful. Positive in 5% of PMM and 87% of AdCa.
BG8	Very useful. Positive in 3%–9% of PMM and 89% of AdCa.
CEA	Very useful. Positive in 81% of AdCa, negative in PMM.
B72.3	Very useful. Positive in 84% of pancreas, 89% of bile duct, 98% of colon AdCa, 0%–3% of PMM.
Ber-EP4	Useful. Positive in >98% of pancreatic and gastric AdCa, 9%–13% of PMM.

Abbreviations: CEA, carcinoembryonic antigen; CK, cytokeratin.

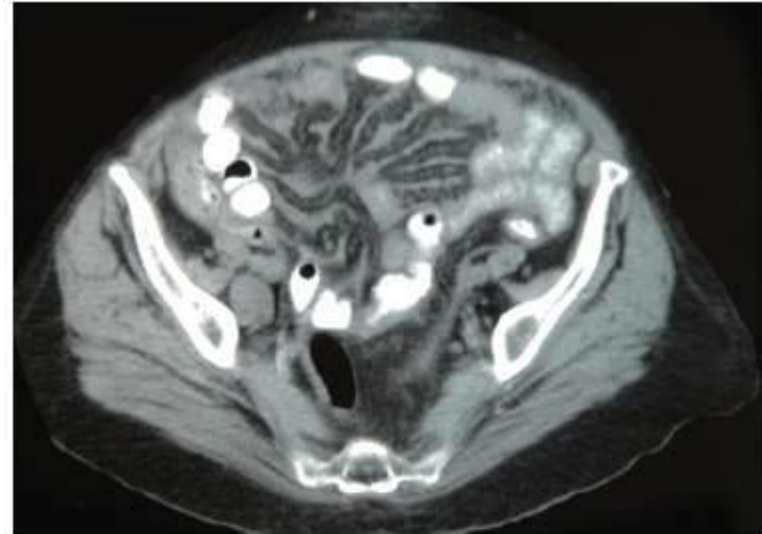
Diagnosis and Staging



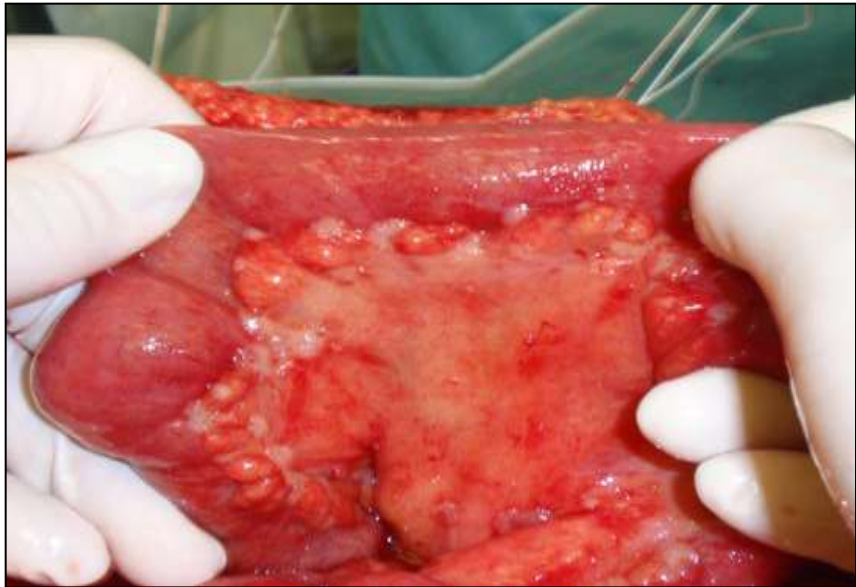
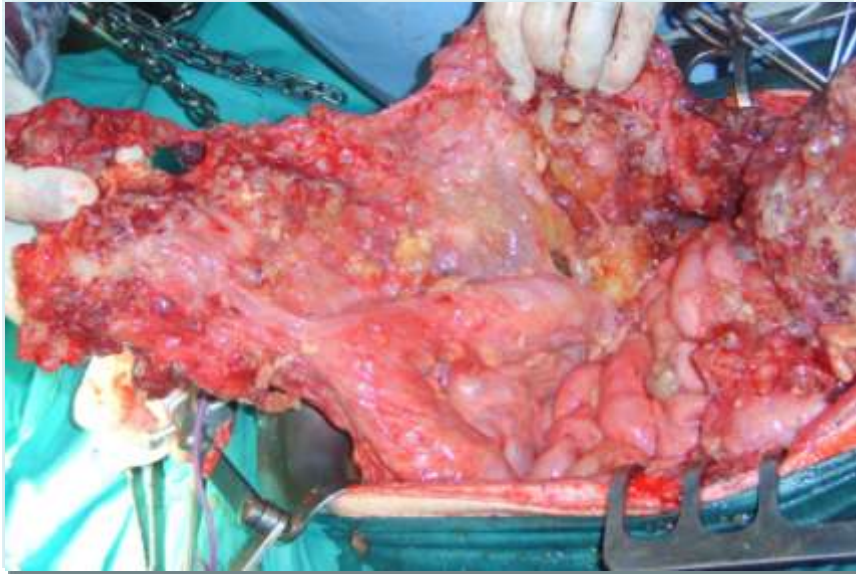
Diagnosis & Staging

Table 1
Classification of symptoms

Classical	Medical	Surgical
Abdominal pain	Abdominal pain	Hernia
Ascites	Weight loss	Ileus
Abdominal mass	Fever	Abdominal perforation
	Diarrhea	
	Vomiting	
	Asthenia	
	Anorexia	



Diagnosis & Staging



Diagnosis & Staging

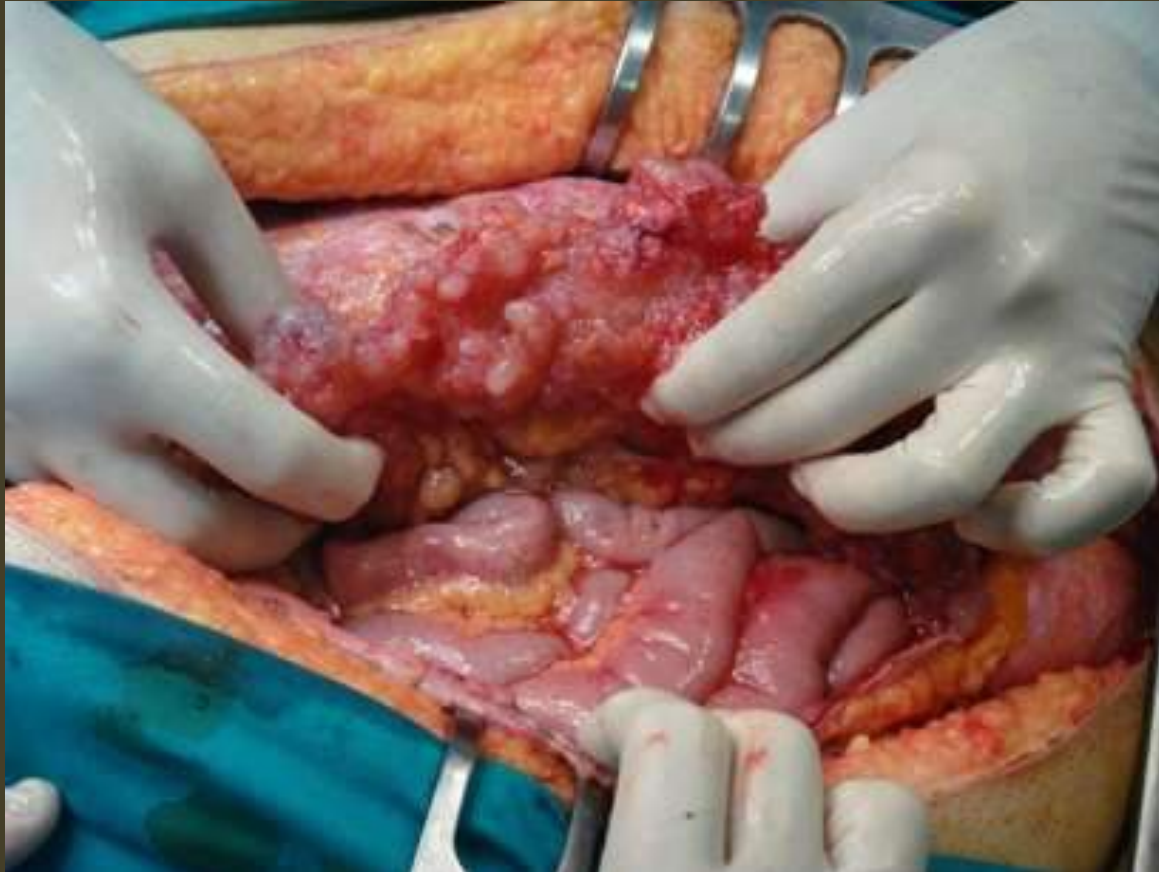
Table 1 Proposed staging system for patients with MPM

Stage	T stage	PCI	N stage*	M stage [#]	5 y OS (%)
I	1	1-10	0	0	87
II	2	11-20	0	0	53
	3	21-30	0	0	
III	4	21-39	0-1	0-1	29
	1-4	1-39	0-1	1	

*N stage, presence of extra-abdominal nodal metastases;

[#]M stage, extra-abdominal metastases. MPM, malignant peritoneal mesothelioma; PCI, peritoneal cancer index; OS, overall survival.

Clinical Results of CRS & HIPEC



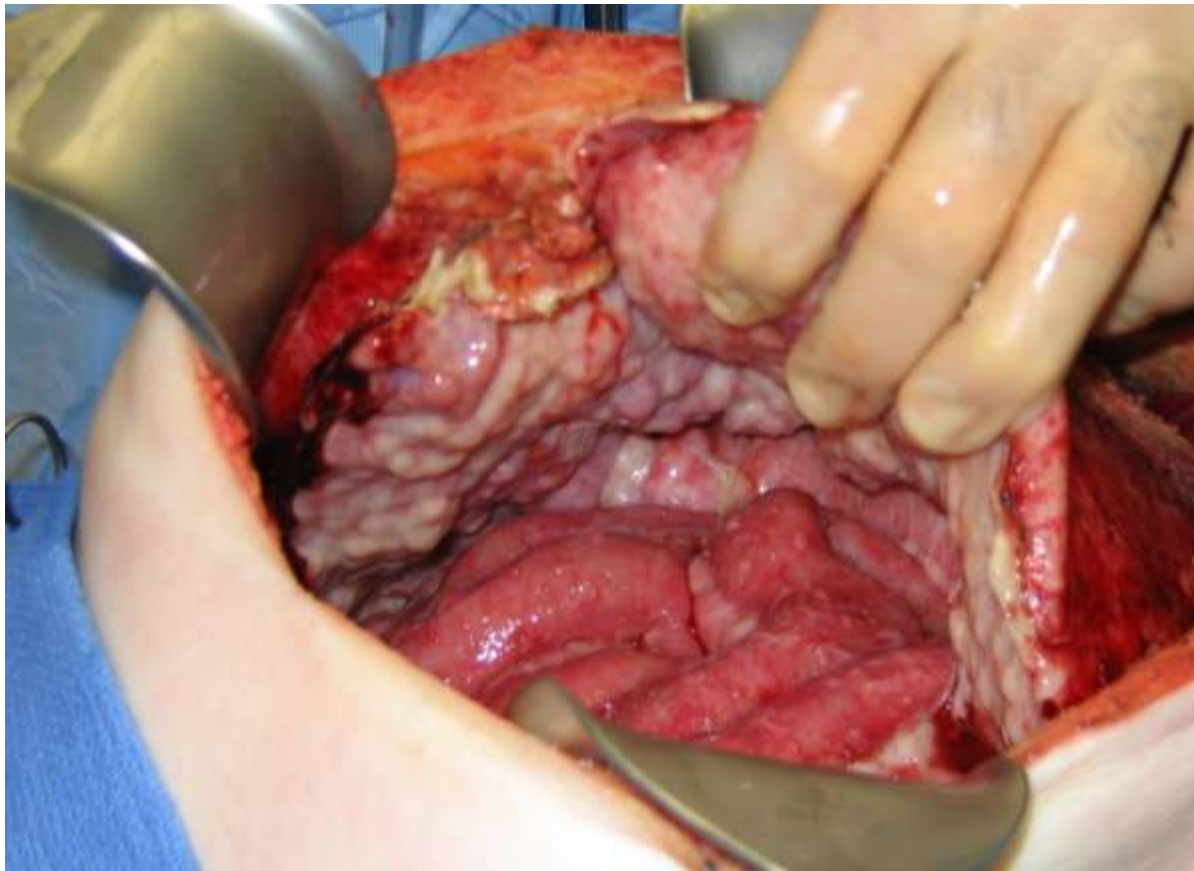
Clinical Results of CRS & HIPEC

Table 1 Selected studies examining overall survival with cytoreduction and hyperthermic Intraperitoneal chemotherapy

Ref.	Year	Era	Sample No.	Age	Gender (female)	HIPEC Agents	Histological Subtype or Grade	Follow-up	Median survival	1 yr	2 yr	3 yr	5 yr	7 yr	10 yr
Park <i>et al</i> ^[33]	1999	1993-1998	18	47	28%	CDDP	9 E, 3 mixed 1 MMF 1 cystic 4 Unk	19	NR		80				
Loggie <i>et al</i> ^[112]	2001		12	51 ¹	8%	MMC	Not stated	45.2	34.2	60	60	50	33	33	
Feldman <i>et al</i> ^[48]	2003	1993-2002	49	47	43%	CDDP	26 E, 4 S 16 TP 1 adenomatoid	28.3	92	86	77	59	59		
Costamagna <i>et al</i> ^[61]	2003	1995-2003	24			CDDP + DOXO, single agent MMC or DOXO			40	78	70	70	52		
Brigand <i>et al</i> ^[6]	2006	1989-2004	15	53.6	29%	CDDP + MMC	12 E, 2 B 1 MC	46.7	35.6	69.3	57.7	43.3	28.9		
Elias <i>et al</i> ^[60]	2007	1996-2005	26	46 ¹	46%	oxaliplatin + irinotecan, single agent oxaliplatin or DOXO	13 E, 1 B 11 TP, 1 MC	55	100	88	83	68	63		
Gómez Portilla <i>et al</i> ^[113]	2007	1998-2005	7	50 ¹	43%	CDDP + DOXO, single agent MMC or oxaliplatin	5 E, 2 B	11	NR	43	43	43	43		
Hesdorffer <i>et al</i> ^[55]	2008	1997-2000	27	53 ¹	26%	CDDP + MMC	23 E, 4 S		70			67%			
Passot <i>et al</i> ^[114]	2008	1989-2006	22			CDDP + MMC	16 E, 3 B 3 MC	47	36.9	69	62	52	31		
Chua <i>et al</i> ^[115]	2009	1997-2008	20	55.7 ¹	30%	CDDP + DOXO	16 E, 1 B, 2 S 1 MC	18.1	29.5	78.2		46.3			
Blackham <i>et al</i> ^[89]	2010	1993-2008	34	54.9 ¹	32%	CDDP or MMC	29 E, 4 B 1 Unk	72	40.8	61		56	17		
Kluger <i>et al</i> ^[54]	2010	1997-2004	47	49 ¹	36%	CDDP + MMC	43 E, 4 B	54	54.9	80.9		61.7	48.9		
Cao <i>et al</i> ^[140]	2012	1989-2009	294	50	46%	CDDP + DOXO ²	259 E, 27 B/S 8 Unk	25	67	83	62	52			
Alexander <i>et al</i> ^[47]	2013	1992-2010	211	52	60%	CDDP or MMC	113 High, 54 Low 44 Unk		38.4				41		26
Schaub <i>et al</i> ^[59]	2013	1994-2010	104	50.9	39%	CDDP	90 E, 14B/S	49.4	52			58	46		
Wong <i>et al</i> ^[52]	2013	2004-2012	26	64	38%	CDDP	15 E, 3 B 1 MMF 3 WD, 1 cystic 3 Unk		41.2						
^{NM} Deraco <i>et al</i> ^[37]	2003	1995-2002	19	49 ¹	53%	CDDP + MMC or DOXO	13 E, 1 S, 1 mixed 2WD, 2MC	27	NR			69			
^{NM} Deraco <i>et al</i> ^[39]	2003		28		61%								70		
^{NM} Deraco <i>et al</i> ^[38]	2003		61	51 ¹	49%	CDDP + MMC or DOXO		20					54		
^{NM} Deraco <i>et al</i> ^[40]	2006	1995-2005	49	52 ¹		CDDP + DOXO or MMC	43 E, 6 B	20.3 ¹					57		
^{NM} Deraco <i>et al</i> ^[30]	2013	1995-2011	116	54.4 ¹	48%	CDDP + DOXO or MMC	105 E, 11 B/S	32.9 ¹					49		
^{NM} Baratti <i>et al</i> ^[50]	2007	1997-2005	60	53.5	60%		43 E, 6 B 5 MC, 6 P	23					53.7		
^{NM} Baratti <i>et al</i> ^[56]	2007	1995-2006	12	38	100%	CDDP + DOXO	4 MC, 8 WD	27	NR				90		

Clinical Results of CRS & HIPEC

^{NM} Baratti <i>et al</i> ^[55]	2010	1996-2008	83	54	55%	CDDP + MMC or DOXO	72 E, 10 B, 1 S	52	44			49.5	45.5
^{NM} Baratti <i>et al</i> ^[54]	2013	1996-2012	108	56.5	46%	CDDP + DOXO or MMC	93 E, 14 B, 1 S	48.8	63.2			52.4	44.6
^{WC} Yan <i>et al</i> ^[46]	2006		100	50 ¹	40%	CDDP + DOXO	86 E, 7 B/S	48	52	78	55	46	39
							7 Unk						
^{WC} Yan <i>et al</i> ^[44]	2007	1989-2005	70	47 ¹	43%	CDDP + DOXO	65 E, 5 B	35	59	82	67	57	49
^{WC} Yan <i>et al</i> ^[46]	2007	1989-2005	62	47 ¹	45%	CDDP + DOXO	57 E, 5 B	37	79	84		58	50
^{WC} Yan <i>et al</i> ^[47]	2009	1989-2009	401	50 ¹	44%	CDDP + DOXO ² or MMC, single agent CDDP or MMC	318 E, 48 B/S	33	53	81		60	47
							35 Unk						
^{WC} Yan <i>et al</i> ^[46]	2011	1989-2009	294	50 ¹	46%	CDDP + DOXO ²	259 E, 27 B/S	24	67	83	62	52	
							8 Unk						



Clinical Results of CRS & HIPEC

Table 2 Prognostic factors in cytoreduction and hyperthermic intraperitoneal chemotherapy procedures

Ref.	Year	Sample No.	Prognostic factors overall survival (multivariate only)
Deraco <i>et al</i> ^[38]	2003	61	Completeness of cytoreduction
Feldman <i>et al</i> ^[48]	2003	49	¹ No prior debulking, deep invasion, age > 60, residual disease > 1 cm
Nonaka <i>et al</i> ^[51]	2005	35	Completeness of cytoreduction, low mitotic count, lower nuclear grade
Deraco <i>et al</i> ^[40]	2006	49	Completeness of cytoreduction, low mitotic count/50 HPF
Yan <i>et al</i> ^[45]	2006	100	No lymph node metastasis, female gender, epithelial type, adequate cytoreduction
Baratti <i>et al</i> ^[20]	2007	60	¹ High-grade histology, WHO performance status > 0, Inadequate cytoreduction
Yan <i>et al</i> ^[41]	2007	62	Mesothelioma nuclear size
Yan <i>et al</i> ^[42]	2009	401	Epithelial subtype, absence of lymph node metastasis, completeness of cytoreduction 0/1, HIPEC
Baratti <i>et al</i> ^[35]	2010	83	Pathologically negative lymph nodes, epithelial subtype, mitotic count ≤ 5/50 HPF, Completeness of cytoreduction
Kluger <i>et al</i> ^[54]	2010	47	¹ Biphasic histological subtype
Yan <i>et al</i> ^[43]	2011	294	¹ Biphasic/sarcomatoid subtype, completeness of cytoreduction score of 2/3, proposed TNM Stage II or III
Cao <i>et al</i> ^[46]	2012	294	Female gender, TNM staging
Baratti <i>et al</i> ^[53]	2012	60	Complete parietal peritonectomy, complete cytoreduction, negative lymph nodes, Epithelial histology, low MIB-1 index
Alexander <i>et al</i> ^[47]	2013	211	Age < 60 yr, R0-1 vs R2-3, low histologic grade, use of cisplatin vs mitomycin-C
Baratti <i>et al</i> ^[34]	2013	108	Epithelial histology, histologically negative lymph nodes, Ki-67 < 10%
Deraco <i>et al</i> ^[50]	2013	116	Histological subtype, completeness of cytoreduction, absence of morbidity 3-5 grade
Schaub <i>et al</i> ^[59]	2013	104	Histological subtype, pre-CRS PCI, preoperative serum CA-125
Wong <i>et al</i> ^[52]	2013	29	Lower peritoneal carcinoma index, completeness of cytoreduction
Pillai <i>et al</i> ^[58]	2013	33	Presence of nuclear estrogen receptor beta

¹Variables that have negatively impacted overall survival.

Clinical Results of CRS & HIPEC

International PSOGI Registry on Peritoneal Mesothelioma



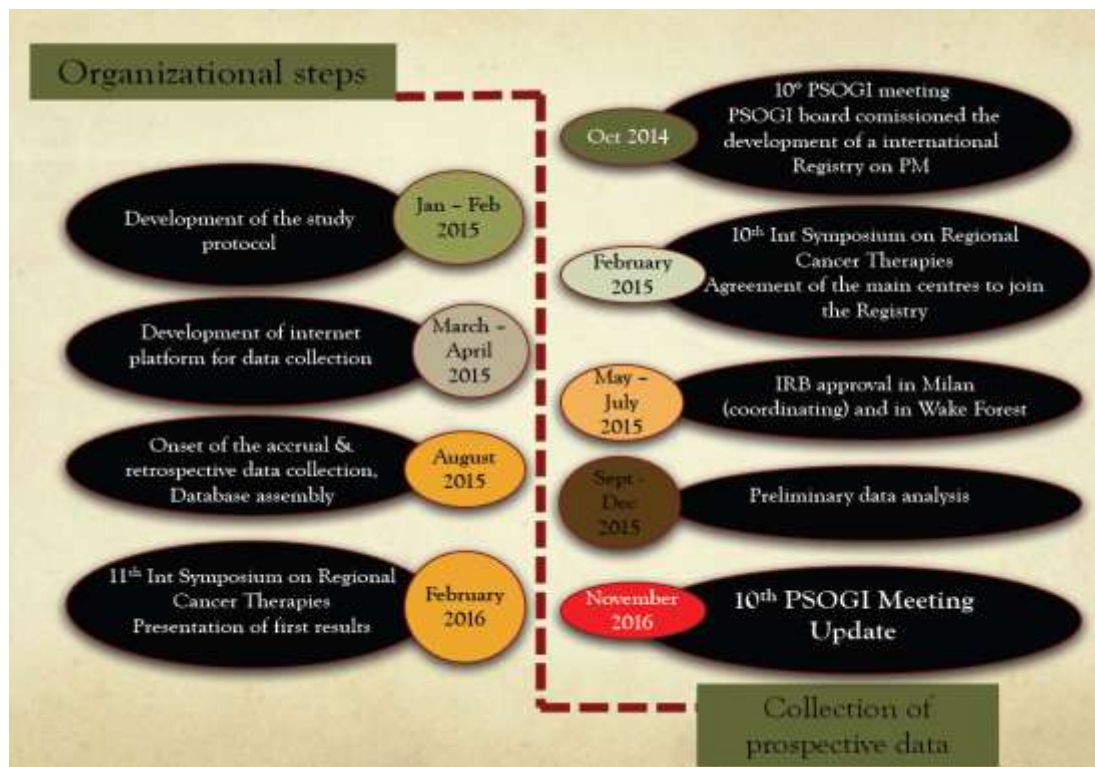
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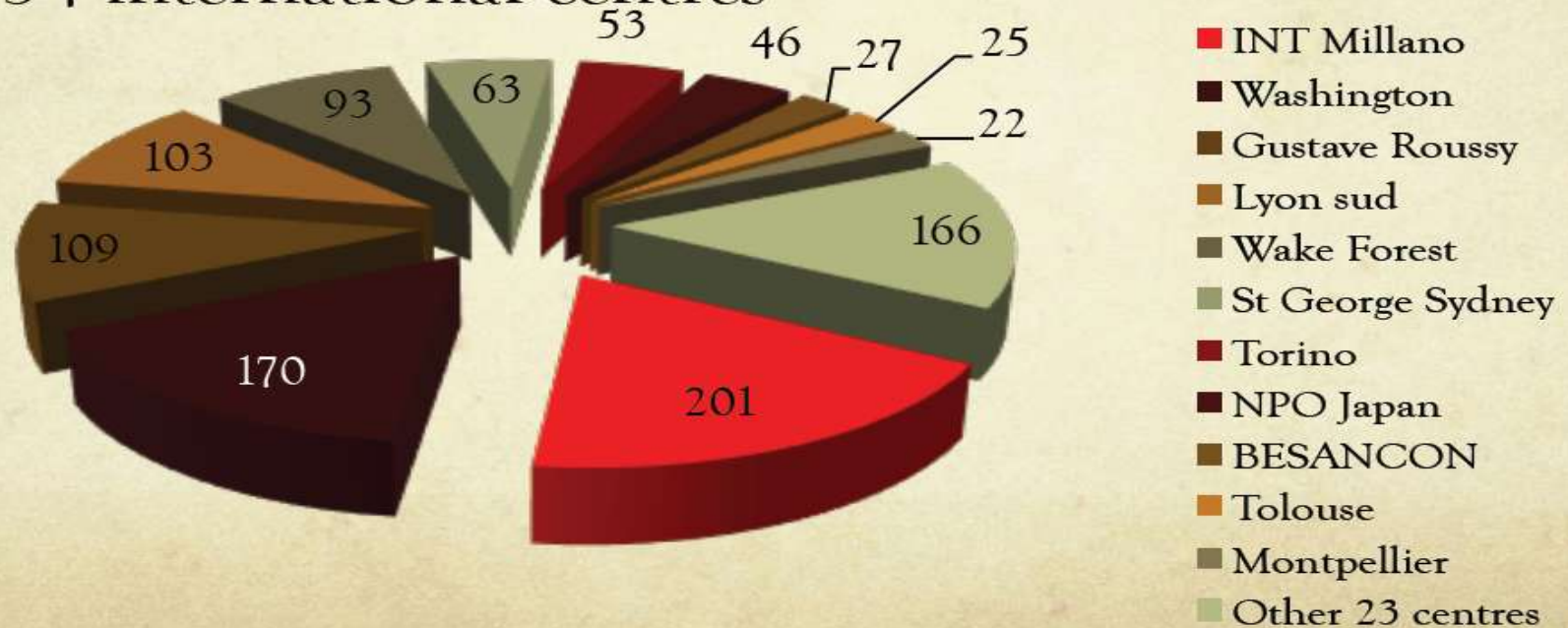
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Clinical Results of CRS & HIPEC

Patients and methods

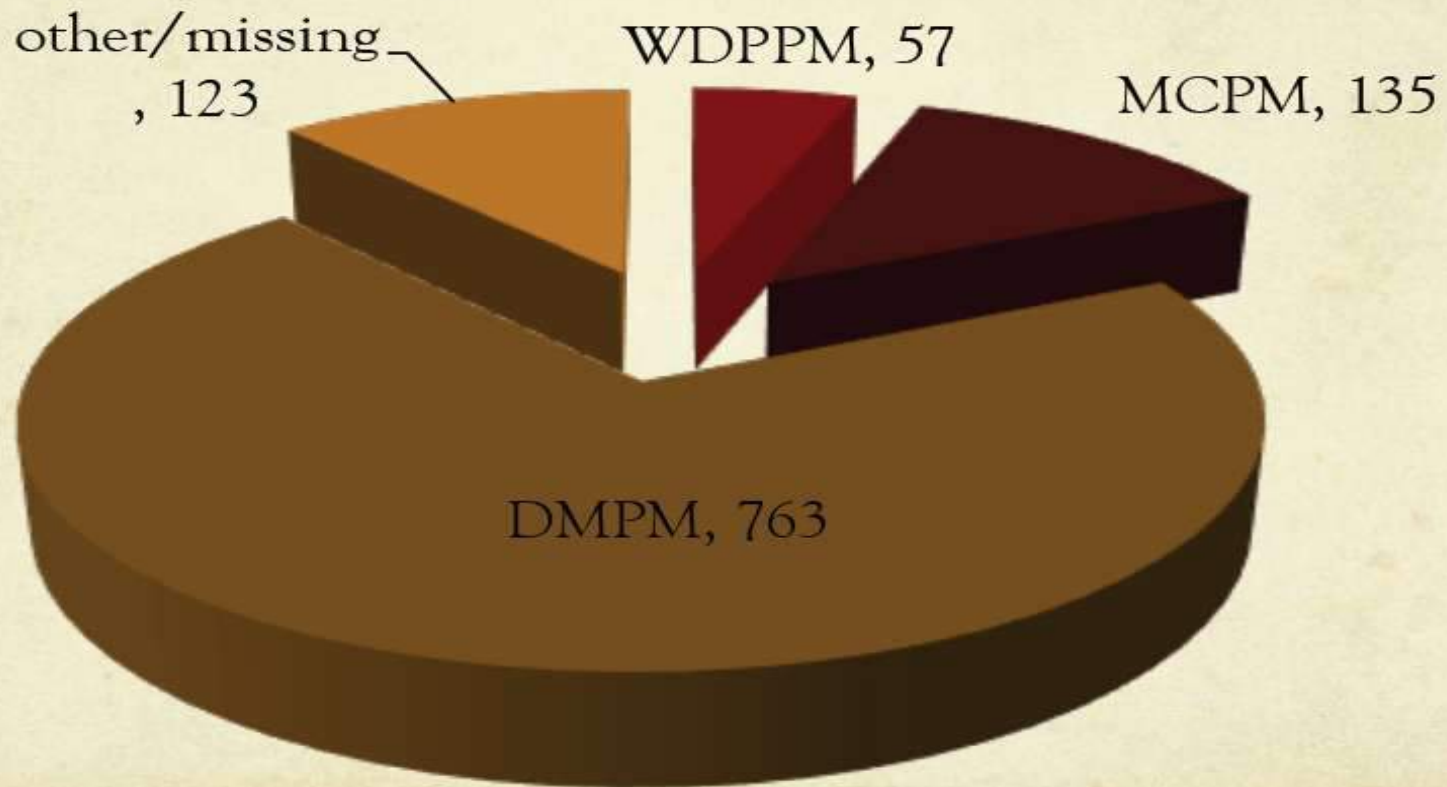
- 1,078 PM patients submitted to 1,211 treatments
- December 1981 to August 2016
- 34 international centres



Clinical Results of CRS & HIPEC

Results (n=1,078)

Histological type distribution

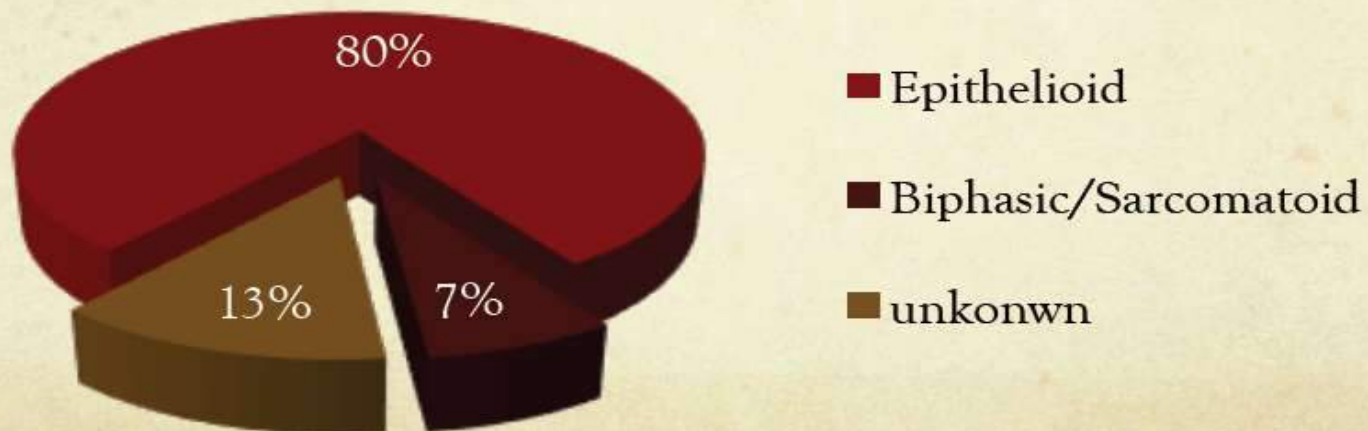


Clinical Results of CRS & HIPEC

Surgically treated DMPM patients (n=763)

- Mean peritoneal cancer index (PCI): 20.1 (SD: 10)

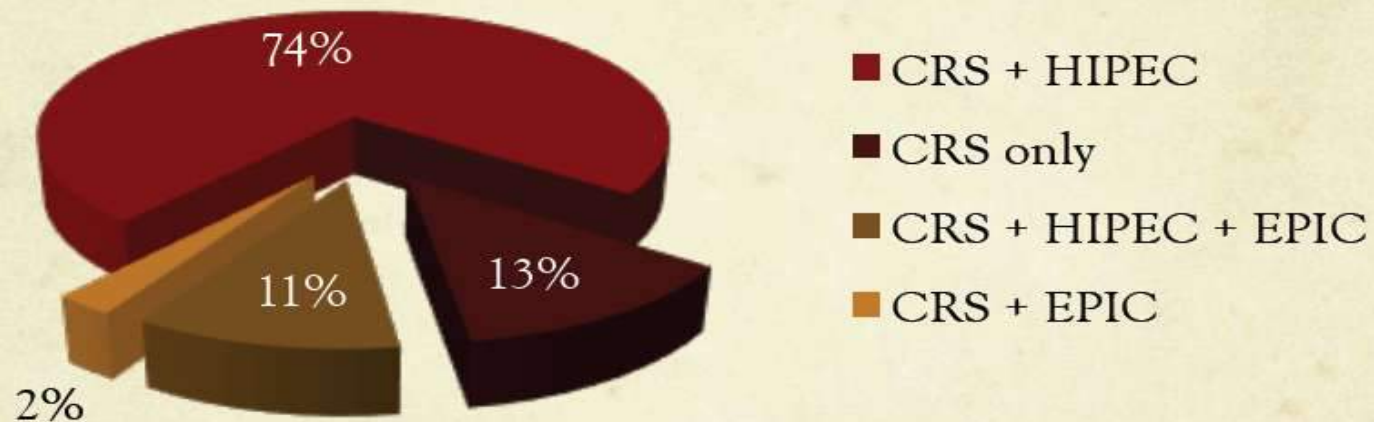
- Histological subtype distribution



Clinical Results of CRS & HIPEC

Surgically treated DMPM patients (n=763)

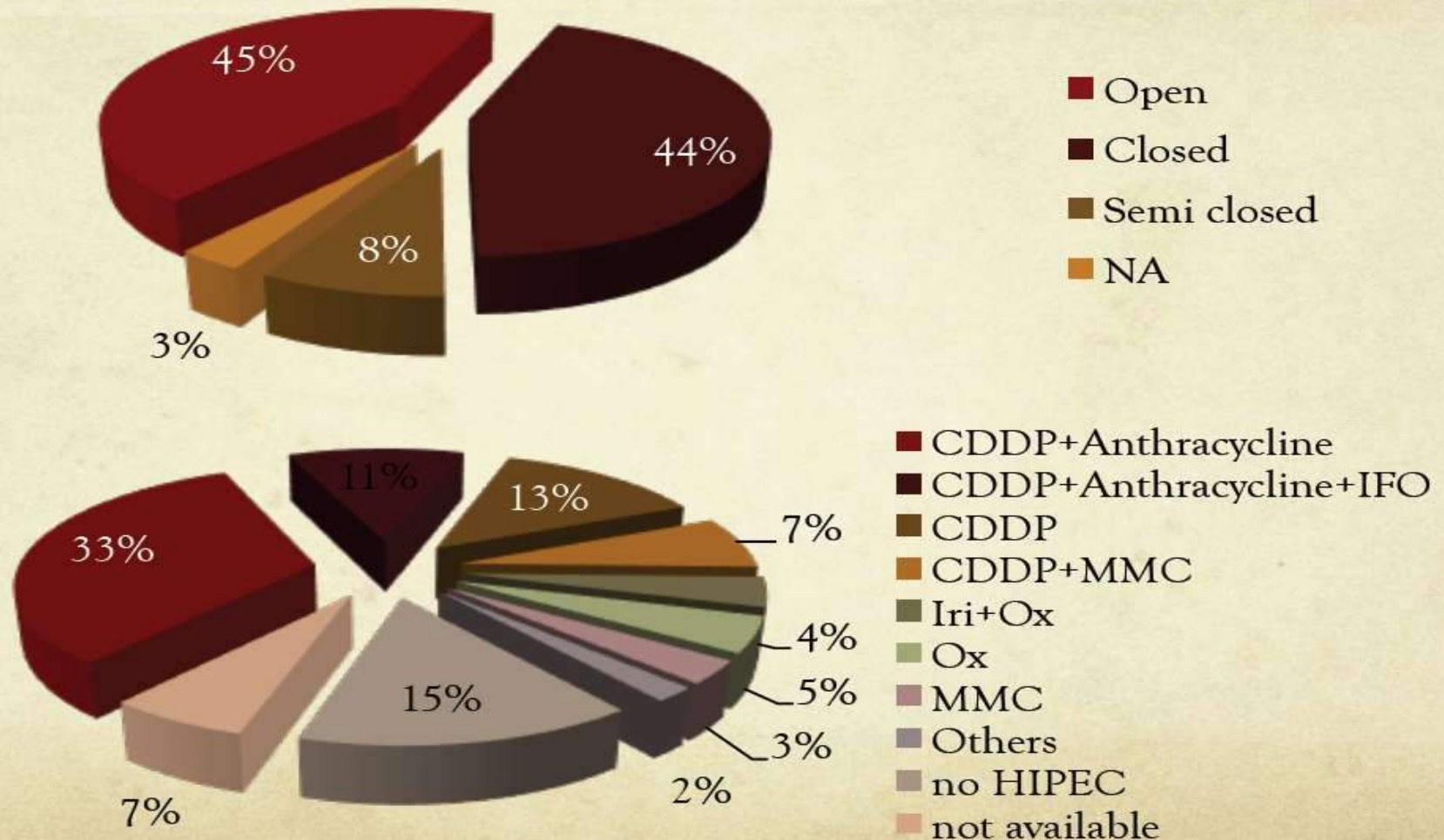
- 216 (34.1%) previous systemic chemotherapy
- Treatment type distribution



- Complete cytoreduction rate: 65.5%
- Mean operating time: 289 minutes (60-720)

Clinical Results of CRS & HIPEC

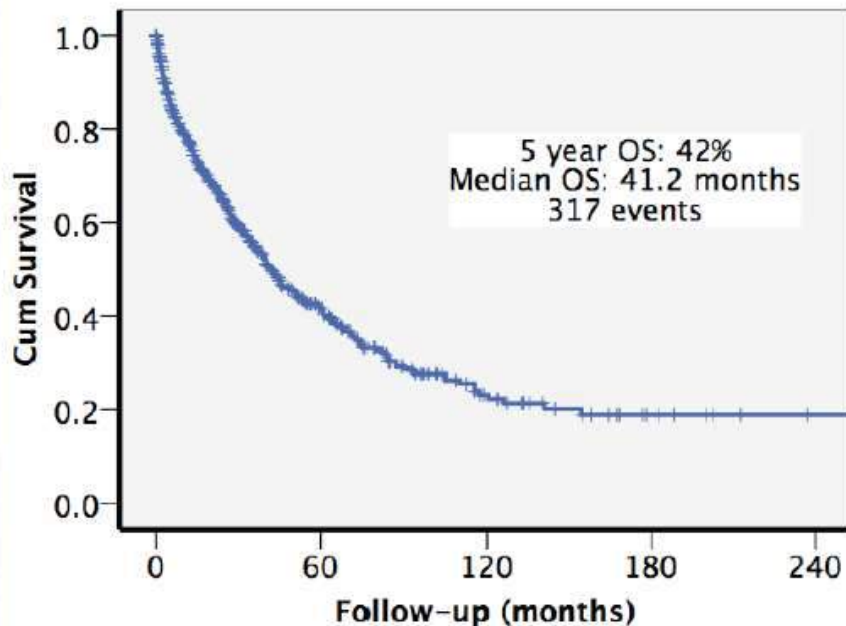
HIPEC



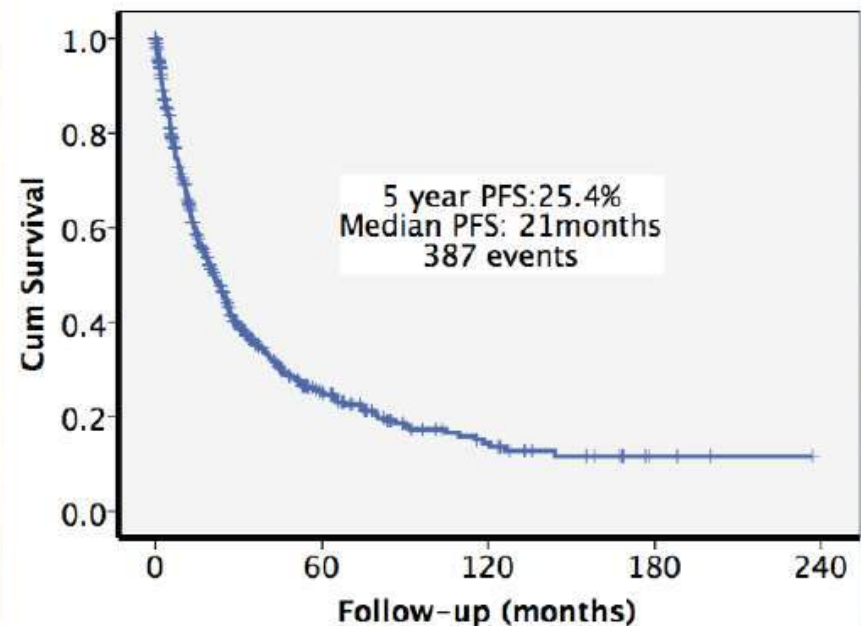
Clinical Results of CRS & HIPEC

Overall and progression free survivals in developing set

Overall Survival (Developing set)



Progression Free Survival (Developing set)



Clinical Results of CRS & HIPEC

Multivariate Cox regression analysis (OS)

Variables	HR	95%CI		p-value
		Lower	Upper	
Age	1.020	1.011	1.030	0.000
PCI	1.024	1.009	1.040	0.002
Histo subtype (epith vs biph/sarc)	1.509	0.990	2.301	0.056
Complete cytoreduction	0.496	0.372	0.660	0.000
Platin-based HIPEC	0.727	0.533	0.992	0.044
G3-5 morbidity	1.399	1.067	1.834	0.015
Case number	0.993	0.989	0.998	0.003

CONCLUSIONS

- Peritoneal mesothelioma is a spectrum disease
- Importance of a expert pathologist
- Systemic chemotherapy : median survival : 8 months
- CRS + HIPEC : promising results
- Prognostic factors : age, PCI, CCR, experience
- But : still survival benefit with R2 resections !
- TEAMWORK (pathologist, surgeon, ICU, nursing staff,.....)

Thank You (for your attention, help, friendship,...)

