

2nd Indonesian Colorectal Conference, 3 Oct 10

Role of Surgery in Advanced Colorectal Cancer



R Sim

TTS Hospital, Singapore





Palliative Surgery

The feasibility of an operation is not the best indication for its performance

Henry Cohen 1900-1977



Palliative Surgery

The lesser the indication,
the greater the complication.

Moshe Schein

situ

- Resection for recurrent or persistent disease after primary treatment failure

Palliative Surgery

Latter two – definitive, preop. intent is cure and increased survival, often also relieve symptoms

Affording relief, not cure...reduce severity of

- Surgery to relieve symptoms knowing in advance that all of the tumour cannot be removed
- Resection with gross or microscopic residual tumour left in-situ
- Resection for recurrent or persistent disease after primary treatment failure

Latter two – definitive, preop. intent is cure and increased survival, often also relieve symptoms

Tissue sampling

Vascular access

Enteral feeding tubes

Palliative Surgery

- Palliative (relief symptoms)

Relief obstruction/bleeding/fistula

Drain effusions

Pain control


Debulk/toilet/devascularise

- Supportive (part of multidisciplinary plan)

Tissue sampling

Vascular access

Enteral feeding tubes



Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients - Ruo et al, J Am Coll Surg 2003;196:722-8.

N=127

Op mortality 1.6%, morbidity 20%, survival 16 months

Non-op - survival 9 months; 8.7% subsequently required op., 1/3 for obstruction

Selection - One site, Liver only, less than 25% involved



Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer - Kleespies et al, Int J Colorectal Dis. 2009;24:1097-109.

N=233

Palliative resection is associated with a particularly unfavorable outcome in rectal cancer patients presenting with a locally advanced tumor (pT4, expected R2 resection) or an extensive comorbidity, and in all CRC patients who show a hepatic tumor load >50%. For such patients, surgery might be contraindicated unless the tumor is immediately life-threatening.



Bowel obstruction

Favourable factors

- Well-nourished
- Early stage, low-grade initial lesion

Odds of benign obstructive process higher in the 12-18 months after resection if extensive carcinomatosis not initially present

- Long interval from first operation - more than 5 years



Bowel obstruction

Unfavourable factors

- Carcinomatosis
- Multiple level obstruction with prolonged transit
- Previous RT to abdomen or pelvis
- Palpable masses
- Ascites requiring frequent drainage
- Cachetic, older patients (5x higher op mortality)
- Poor performance status, low albumin
- Liver and distant metastases

Non-operative options

- Laser
- Endoluminal stent
- Radiotherapy
- Chemotherapy
- Palliative medicine





Evaluation of endpoints

- Primary

QOL - relief/prevent symptoms

Morbidity of procedure, relative to estimated survival

Morbidity of not doing procedure

Mode of death with and without intervention

Cost analysis

- Secondary

Survival benefit

QOL of caregivers with and without intervention



Conclusions

- There is a definite role for palliative surgery

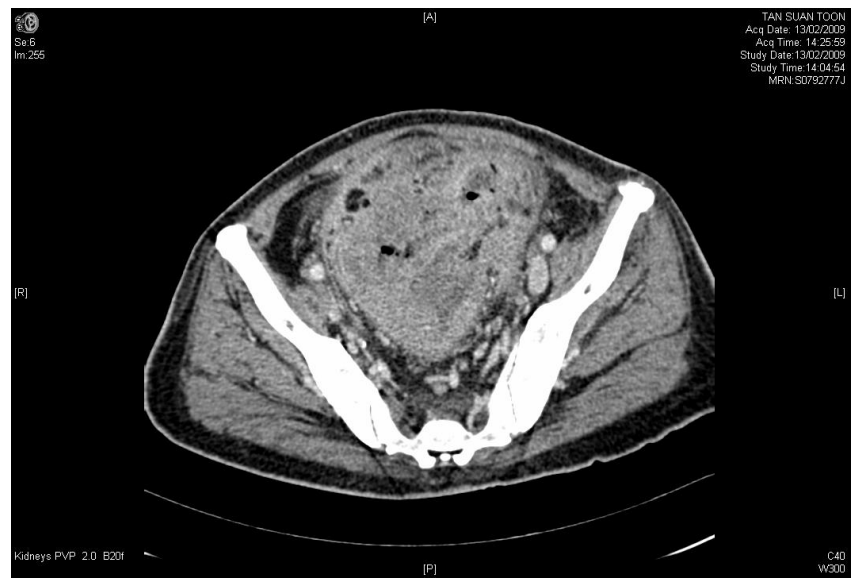
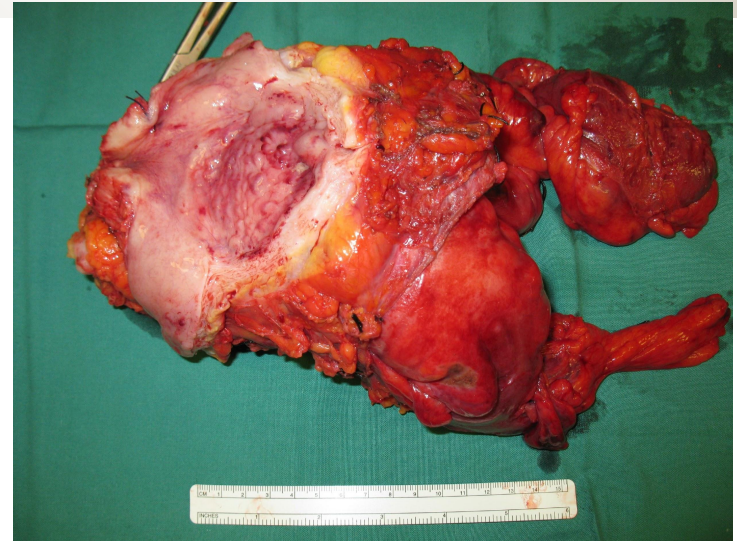
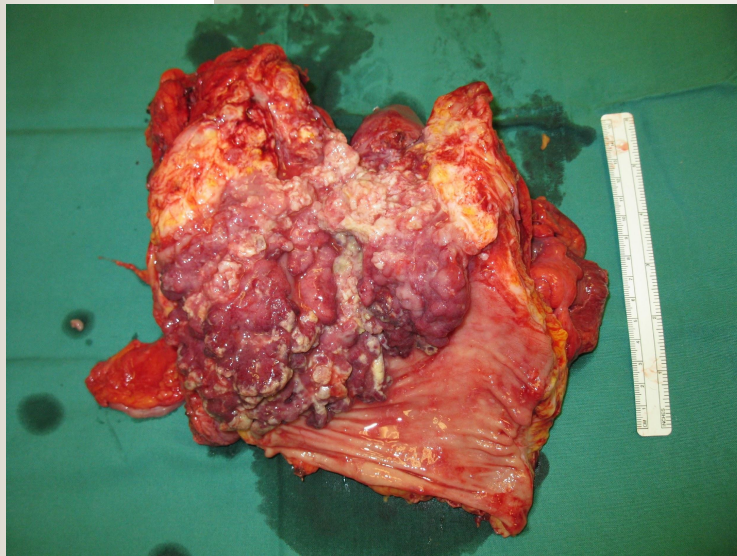
- Palliative surgery must be safe and efficacious

- The key is patient selection:

Patient factors - op. risk, QOL, estimated survival

Disease factors - tumour burden

Technical factors





Population-based assessment of the surgical management of locally advanced colorectal cancer.

Govindarajan et al, J Natl Cancer Inst 2006;98:1474-81.

N=8380

The majority(2/3) of patients with locally advanced colorectal cancer did not receive a multivisceral resection.

Compared with standard resection, multivisceral resection was associated with improved overall survival for patients with colon (hazard ratio [HR] = 0.89, 95% confidence interval [CI] = 0.83 to 0.96) and rectal (HR = 0.81, 95% CI = 0.70 to 0.94) cancer, with no associated increase in early mortality.



Long-Term Follow-up after Surgery for Advanced
Colorectal Carcinoma Involving the Urogenital Tract.
Stief et al, European Urology 2002;5:546-550.

N=101

Malignant infiltration in 52%

Negative margin in 54%

41% morbidity, 5% mortality rate

Five year overall survival was 24.4% (median 23 months)

Removal of bladder and prostate favourable and ureteral removal ominous factor.



Long-Term Follow-up after Surgery for Advanced
Colorectal Carcinoma Involving the Urogenital Tract.
Stief et al, European Urology 2002;5:546-550.

N=101

Conclusion: Multivisceral extirpation of advanced colorectal carcinomas involving the urogenital tract should be recommended in **selected** patients. Our data showed it to be a safe surgical procedure, which is associated with favourable long-term outcome in **non-metastatic** patients in whom **complete resection** could be achieved.




Oncologic Contraindications to Liver Resection

Relative

- Extrahepatic disease
- Colonic recurrence
- Solitary resectable peritoneal metastasis
- Hilar lymph node metastases

Absolute

- Peritoneal carcinomatosis
- Multiple extrahepatic mets
- Inability to perform hepatic R0 resection

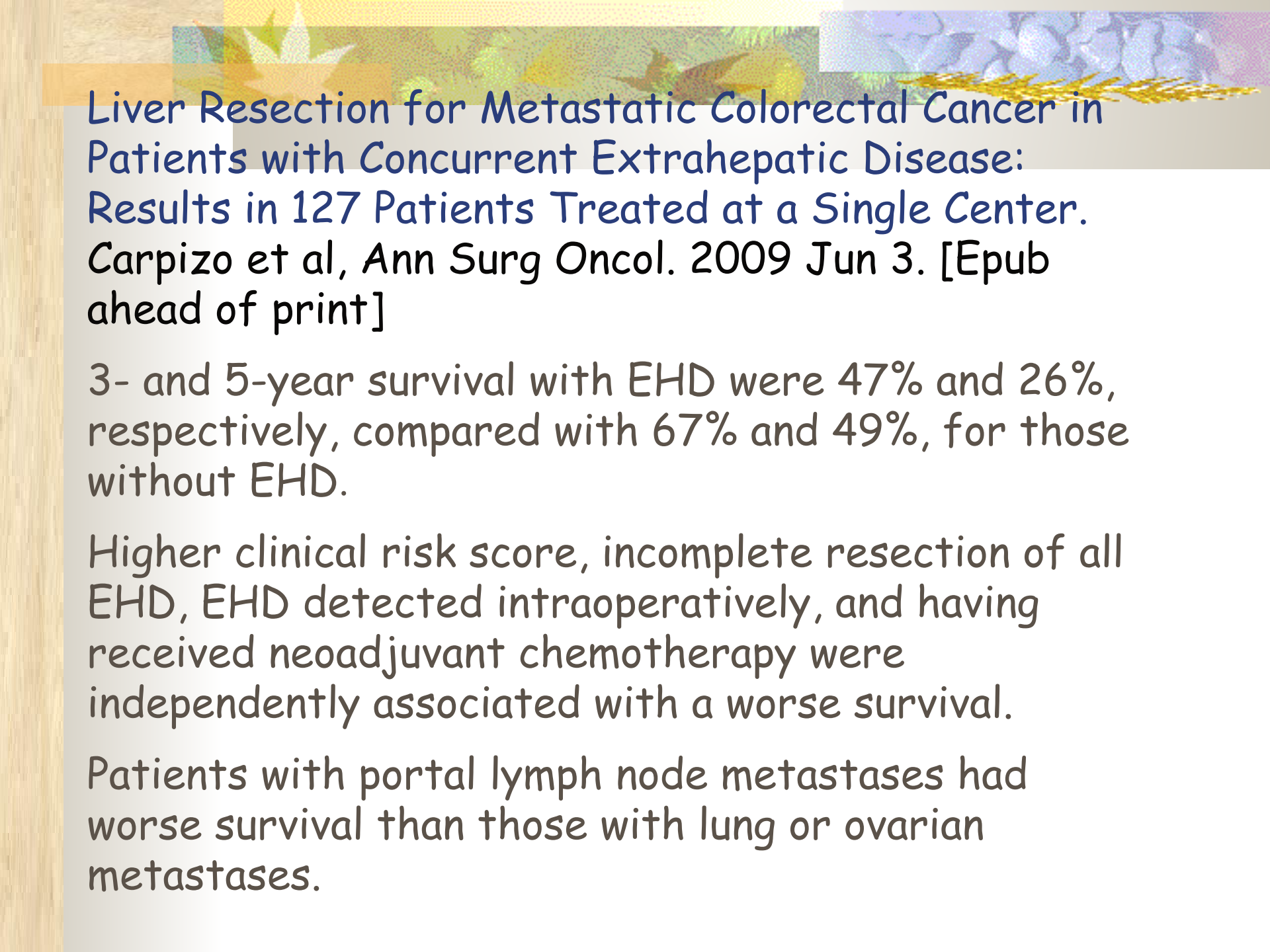


The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. Verhoef et al, Dis Colon Rectum 2009; 52:23-30.

N=23

Chemo, Liver resection, CRT, rectal resection

It allows most patients (3/4) to undergo curative resections of both metastatic and primary disease and can avoid useless rectal surgery in patients with incurable metastatic disease.




Liver Resection for Metastatic Colorectal Cancer in Patients with Concurrent Extrahepatic Disease: Results in 127 Patients Treated at a Single Center. Carpizo et al, Ann Surg Oncol. 2009 Jun 3. [Epub ahead of print]

3- and 5-year survival with EHD were 47% and 26%, respectively, compared with 67% and 49%, for those without EHD.

Higher clinical risk score, incomplete resection of all EHD, EHD detected intraoperatively, and having received neoadjuvant chemotherapy were independently associated with a worse survival.


Patients with portal lymph node metastases had worse survival than those with lung or ovarian metastases.



Liver Resection for Metastatic Colorectal Cancer in Patients with Concurrent Extrahepatic Disease: Results in 127 Patients Treated at a Single Center. Carpizo et al, Ann Surg Oncol. 2009 Jun 3. [Epub ahead of print]

CONCLUSION: Concurrent resection of hepatic and EHD in well-selected patients is associated with a possibility of long-term survival. The presence of limited and resectable EHD should not be an absolute contraindication to resection. The site of EHD and the nearly universal recurrence rate must be taken into consideration.

Among patients who had a complete resection of all disease, 95% recurred.




Outcomes associated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy in colorectal cancer patients with peritoneal surface disease and hepatic metastases. Varban et al, Cancer. 2009 Jun 4. [Epub ahead of print].

N=142, 14 had HM

The median overall survival for patients with HM was 23.0 months. Two-year and 4-year survival rates were 43.3% and 14.4%, respectively. Patients without HM had 2-year and 4-year survival rates of 36.8% and 17.4%, respectively. Overall survival was not significantly different for patients with and without HM.

Most patients had a single small lesion treated with a minor hepatic resection.



Peritoneal carcinomatosis and liver metastases from colorectal cancer treated with cytoreductive surgery perioperative intraperitoneal chemotherapy and liver resection. Chua et al, Eur J Surg Oncol. 2009 Jul 23. [Epub ahead of print]

N=55, 16 also had liver mets

Overall median survival was 36 months. No difference in survival between CRPC alone or CRPC with LM, but patients with CRPC and LM had a lower PCI ($p=0.03$).

CONCLUSIONS: A curative procedure may be offered to selected patients with CRPC and LM, especially in those with a low peritoneal cancer index.

Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment

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On behalf of the ESMO Guidelines Working Group*

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incidence

In 2006 there were 412 900 new cases of colorectal cancer (CRC) in Europe. This is 12.9% of all cancer cases. CRC was responsible for 217 400 deaths in Europe in 2006. This represents 12.2% of all cancer deaths. Approximately 25% present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC.

diagnosis

Clinical or biochemical suspicion of metastatic disease should always be confirmed by adequate radiological imaging [usually a computed tomography (CT) scan or alternatively magnetic resonance imaging (MRI) or ultrasonography]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan can be useful in determining the malignant characteristics of tumoral lesions, especially when combined with CT scan. FDG-PET scan is especially useful to characterize the extent of metastatic disease when the metastases are potentially resectable. Histology of the primary tumour or metastases is always needed before chemotherapy is started. For metachronous metastases histopathological or cytological confirmation of metastases should be obtained, if the clinical or radiological presentation is atypical or very late after the initial diagnosis of the primary tumour. Resectable metastases do not need histological or cytological confirmation before resection because of a low chance of seeding.

Evaluation of the general condition, organ function and concomitant non-malignant diseases determines the therapeutic strategy for patients with metastatic CRC.

determination of the treatment strategy

The optimal treatment strategy of patients with metastatic CRC should be discussed in a multidisciplinary team.

In order to identify the optimal treatment strategy for patients with metastatic CRC, the staging should include at least clinical examination, blood counts, liver and renal function tests, carcinoembryonic antigen (CEA), CT scan of the abdomen and chest (alternatively, MRI). The general condition and performance status of the patient are strong prognostic and predictive factors. Known biochemical prognostic factors are white blood cell count, alkaline phosphatase level, lactate dehydrogenase, serum bilirubin and albumin. Additional examinations as clinically needed, are recommended before major abdominal or thoracic surgery with potentially curative intent. An FDG-PET can give additional information on equivocal lesions before resection of metastatic disease or can identify new lesions in the case of planned resection of metastases.

treatment of metastatic CRC

The majority of patients have metastatic disease that initially is not suitable for resection. It is, however, important to select patients in whom the metastases are suitable for resection and those with initially unresectable disease in whom the metastases can become suitable for resection after a major response has been achieved with combination chemotherapy. The aim of the treatment in the last group of patients may therefore be to reverse initially unresectable metastatic CRC to resectable CRC.

PRINCIPLES OF SURGERY (1 of 3)

Transanal excision:¹

• Criteria

- ▶ < 30% circumference of bowel
 - ▶ < 3 cm in size
 - ▶ Margin clear (> 3 mm)
 - ▶ Mobile, nonfixed
 - ▶ Within 8 cm of anal verge
 - ▶ T1 only
 - ▶ Endoscopically removed polyp with cancer or indeterminate pathology
 - ▶ No lymphovascular (LVI) or perineural invasion
 - ▶ Well to moderately differentiated
 - ▶ No evidence of lymphadenopathy on pretreatment imaging
- When the lesion can be adequately identified in the rectum, transanal microsurgery may be used.

Transabdominal Resection: Abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision.

• Management Principles

- ▶ The treating surgeon should perform a rigid proctoscopy before initiating treatment
- ▶ Removal of primary tumor with adequate margins
- ▶ Laparoscopic surgery is not recommended outside of a clinical trial
- ▶ Treatment of draining lymphatics by total mesorectal excision
- ▶ Restoration of organ integrity, if possible
- ▶ Surgery should be 5-10 weeks following full dose 5 1/2 wk neoadjuvant chemoradiation

• Total mesorectal excision


- ▶ Reduces positive radial margin rate.
 - ▶ Extend 4-5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, < 5cm from anal verge), negative distal bowel wall margin of 1-2 cm may be acceptable, this must be confirmed to be tumor free by frozen section.
 - ▶ Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.
- Lymph node dissection^{2,3}
- ▶ Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
 - ▶ Extended resection not indicated in the absence of clinically suspected nodes.



Dutch Colorectal Cancer Group

Preop radiotherapy combined with TME for resectable rectal cancer. Kapiteijn et al. N EJM 2001;345: 638-46.

- Estimated local recurrence at 2 years - 2.4% with preop radiotherapy and 8.2% without.
- Survival rate was not significantly different from that in the group treated with TME alone.



'Preoperative radiation can mitigate but not eliminate the adverse effects of imperfect surgery. The best outcomes occurred when preoperative radiation was followed by optimum surgery, but conversely, optimum surgery alone was not the complete answer to local recurrence.'

Wolff

Difference between Nerve-sparing Surgery (NSS,or D 3) and Total Mesorectal Excision (TME)

	NSS or D 3	TME
<i>dissecting layer</i>	<i>parietal fascia</i>	<i>visceral fascia</i>
<i>lateral dissection</i>	<i>yes</i>	<i>no</i>
<i>number</i>	<i>main three types</i>	<i>single</i>
<i>concept</i>	<i>Individualization case-oriented</i>	<i>standardization</i>



Lateral Pelvic Lymphadenectomy

- Results of lateral LN dissection similar to TME with RT
- Low positive lateral LN yield
- Prognostic/therapeutic significance
- Higher morbidity

JCOG 0212

- Phase III, resectable Stage II/III without apparent lateral LN mets
- Evaluate TME vs ANP D3 dissection



Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. Tekkis et al, Lancet Oncology (Sep 2009).

N= 20 studies, 5502 patients from one randomised, three prospective non-randomised, and 14 retrospective case-control studies published between 1984 and 2009.

No significant differences in 5-year survival (hazard ratio [HR] 1.09, 95% CI 0.78-1.50; p=0.62), 5-year disease-free survival (HR 1.23, 95% CI 0.75-2.03, p=0.41), and local (OR 0.83, 95% CI 0.61-1.13; p=0.23) or distant recurrence (OR 0.93, 95% CI 0.72-1.21; p=0.60).



'In the world of Surgical Oncology


Biology is King

Selection is Queen

Technical maneuvers are the Prince and
Princess who frequently try to overthrow
the powerful forces of the King or Queen,

Usually to no long-term avail, although with
some temporary apparent victories.'

Cady



Predictive clinicopathologic factors for limited response of T3 rectal cancer to combined modality therapy. Lin et al. Int J Colorectal Dis 2008; 23:243-249

N= 274 patients

51% downstaging

5-year DFS - 89%(downstaged) vs 45%(not downstaged)

Radial extension on ERUS >2.5 mm, metastatic disease and poorly differentiated pathology associated with limited downstaging.

Combination of SELDI-TOF-MS and Data Mining Provides Early-stage Response Prediction for Rectal Tumors Undergoing Multimodal Neoadjuvant Therapy

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Objective: We investigated whether proteomic analysis of the low molecular weight region of the serum proteome could predict histologic response of locally advanced rectal cancer to neoadjuvant radiochemotherapy (RCT).

Summary Background Data: Proteomic analysis of serum is emerging as a powerful new modality in cancer, in terms of both screening and monitoring response to treatment. No study has yet assessed its ability to predict and monitor the response of rectal cancer to RCT.

Methods: Sequential serum samples from 20 patients undergoing

provided optimal classification accuracy. In more detail, a cohort of 14 protein peaks were identified that collectively differentiated between good and poor responders, with 87.5% sensitivity and 80% specificity.

Conclusions: Serum proteomic analysis may represent an early response predictor in multimodal treatment regimens of rectal cancer. These data suggest that this novel, minimally invasive modality may be a useful adjunct in the multimodal management of rectal cancer, and in the design of future clinical trials.

(Ann Surg 2007;245: 259–266)

Microarray-Based Prediction of Tumor Response to Neoadjuvant Radiochemotherapy of Patients With Locally Advanced Rectal Cancer

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Int J Colorectal Dis (2009) 24:191–200

DOI 10.1007/s00384-008-0616-8

ORIGINAL ARTICLE

The predictive value of metabolic response to preoperative radiochemotherapy in locally advanced rectal cancer measured by PET/CT

**Robert Rosenberg • Ken Herrmann • Ralf Gertler •
Beat Künzli • Markus Essler • Florian Lordick •
Karen Becker • Tibor Schuster • Hans Geinitz •
Matthias Maak • Markus Schwaiger •
Jörg-Rüdiger Siewert • Bernd Krause**

SHORT COMMUNICATION

Locally advanced rectal cancer: histopathological correlation and predictive accuracy of serial MRI after neoadjuvant chemotherapy

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Laparoscopy –The Issues

- Feasibility and safety
- Adequacy - same radical surgery as open op.
- Efficacy - short term benefits and long term oncologic results
- Time and Cost - is it worth the effort?
- Training and certification - who can be accredited?

Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial

Antonio M Lacy, Juan C García-Valdecasas, Salvadora Delgado, Antoni Castells, Pilar Taurá, Josep M Piqué, Josep Visa

Summary

Background Although early reports on laparoscopy-assisted colectomy (LAC) in patients with colon cancer suggested that it reduces perioperative morbidity, its influence on long-term results is unknown. Our study aimed to compare efficacy of LAC and open colectomy (OC) for treatment of non-metastatic colon cancer in terms of tumour recurrence and survival.

Methods From November, 1993, to July, 1998, all patients with adenocarcinoma of the colon were assessed for entry in this randomised trial. Adjuvant therapy and postoperative follow-up were the same in both groups. The main endpoint was cancer-related survival. Data were analysed according to the intention-to-treat principle.

Findings 219 patients took part in the study (111 LAC group, 108 OC group). Patients in the LAC group recovered faster than those in the OC group, with shorter peristalsis-detection ($p=0.001$) and oral-intake times ($p=0.001$), and shorter hospital stays ($p=0.005$). Morbidity was lower in the LAC group ($p=0.001$), although LAC did not influence perioperative mortality. Probability of cancer-related survival was higher in the LAC group ($p=0.02$). The Cox model showed that LAC was independently associated with reduced risk of tumour relapse (hazard ratio 0.39, 95% CI 0.19–0.82), death from any cause (0.48, 0.23–1.01), and death from a cancer-related cause (0.38, 0.16–0.91) compared with OC. This superiority of LAC was due to differences in patients with stage III tumours ($p=0.04$, $p=0.02$, and $p=0.006$, respectively).

Interpretation LAC is more effective than OC for treatment of colon cancer in terms of morbidity, hospital stay, tumour recurrence, and cancer-related survival.

Lancet 2002; **359**: 2224–29

Departments of Surgery (A M Lacy MD, J C García-Valdecasas MD, S Delgado MD, J Visa MD), **Gastroenterology** (A Castells MD, J M Piqué MD), and **Anaesthesia** (P Taurá MD), **Institut de Malalties Digestives, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, 08036 Barcelona, Spain**

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Introduction

Colorectal cancer is the second leading cause of cancer-related death in Western countries. Prognosis associated with this disease has improved due to early diagnosis and changes in medical therapy. Adjuvant chemotherapy in colon cancer, radiotherapy, and introduction of the total mesorectal excision technique in rectal cancer have increased survival, especially in patients with stage III tumours. Moreover, oxaliplatin and irinotecan have improved the prognosis associated with metastatic colorectal cancer.¹

Laparoscopic surgery has led to great progress in the treatment of many gastrointestinal diseases.² Early reports on laparoscopy-assisted colectomy (LAC) in patients with colon cancer suggest that it lowers surgical trauma, decreases perioperative complications, and leads to more rapid recovery.^{3–6} However, development of port-site metastases in some cases showed that this approach was questionable.^{7,8}

Few preliminary data that compare LAC with open colectomy (OC) in colon cancer have been reported. They suggest that LAC is associated with reduced perioperative morbidity and very low risk of wound metastasis.^{4,9,10} However, there are no studies that compare LAC and OC in terms of tumour recurrence and survival.

In this article we report the results of a randomised trial in patients with non-metastatic colon cancer. The aim of the trial was to assess whether there are differences in cancer-related survival between LAC and OC.

Methods

Patients

From November, 1993, to July, 1998, all patients admitted to our unit with adenocarcinoma of the colon, 15 cm above the anal verge, were assessed. Exclusion criteria were: cancer located at the transverse colon, distant metastasis, adjacent organ invasion, intestinal obstruction, past colonic surgery, and no consent to participate in the study.

Randomisation was done the day before surgery. Patients were stratified in two groups according to tumour location (right or left side, with respect to the splenic flexure), and subsequently assigned to LAC or OC by means of sealed opaque envelopes containing computer-generated random numbers. To prevent selection bias, random numbers were generated by an investigator (AC) who was not involved in enrolment of participants.

Due to the limited evidence about LAC at the beginning of the study, interim analyses that assessed early morbidity, tumour recurrence, and port-site metastasis were planned during the first period.^{9,10} The study was approved by the institutional ethics of research committee and oral consent was obtained from each patient.

Interpretation LAC is more effective than OC for treatment of colon cancer in terms of morbidity, hospital stay, tumour recurrence, and cancer-related survival.

This superiority of LAC was due to differences in patients with stage III tumours

Randomised controlled trials

TABLE 1 Trials Comparing Laparoscopic with Open Colectomy

Trial	Randomized Arms		
	Laparoscopic	Open	Conversion
Barcelona	111	108	12 (11%)*
COSTSG†	435	437	90 (21%)
COLOR‡	627	621	91 (17%)
CLASICC§	526	268	143 (29%)

*Indicates "tumor-related" for the Barcelona trial.
 †COSTSG = Clinical Outcomes of Surgical Therapy Study Group.
 ‡COLOR = Colon Carcinoma Laparoscopic or Open Resection.
 §CLASICC = Conventional Versus Laparoscopic-assisted Surgery in Colorectal Cancer.

TABLE 2 A Comparison of Patient-related Benefits in Trials Comparing Laparoscopic with Open Colectomy

Trial	Morbidity		Mortality		Length of								
	Laparoscopic	Open	Laparoscopic	Open	Incision (mm)		Surgery (min)		Ileus		Hospital Stay		
					Laparoscopic	Open	Laparoscopic	Open	Laparoscopic	Open	Laparoscopic	Open	
Barcelona	12 (11%)	31 (29%)	19 (18%)	27 (26%)	45 left, 65 right		n/a	142	118	54 hours§	85 hours	5.2 days	7.9 days
COSTSG*	92 (21%)	85 (20%)	2 (<1%)	4 (1%)	60	180	150	95	n/a	n/a	5 days	6 days	
COLOR†	111 (21%)	110 (20%)	6 (1%)	10 (2%)	n/a	n/a	145	115	2.9 days¶	3.8 days	8.2 days	9.3 days	
CLASICC‡	67 (13%)	29 (11%)	21 (4%)	13 (5%)	100	220	180#	135#	6 days**	6 days	9 days	11days	



Meta-analyses on LARR

- Gao F, Cao YF, Chen LS. Meta-analysis of short-term outcomes after laparoscopic resection for rectal cancer. *Int J Colorectal Dis* 2006;21:652-656.

11 studies, 1995-2005, n=285

- Aziz O, Constantinides V, Tekkis PP, et al. Laparoscopic vs open surgery for rectal cancer: a meta-analysis. *Ann Surg Oncol* 2006;13:413-424.

20 studies, 1993-2004, n=909(lap), 1162(open)

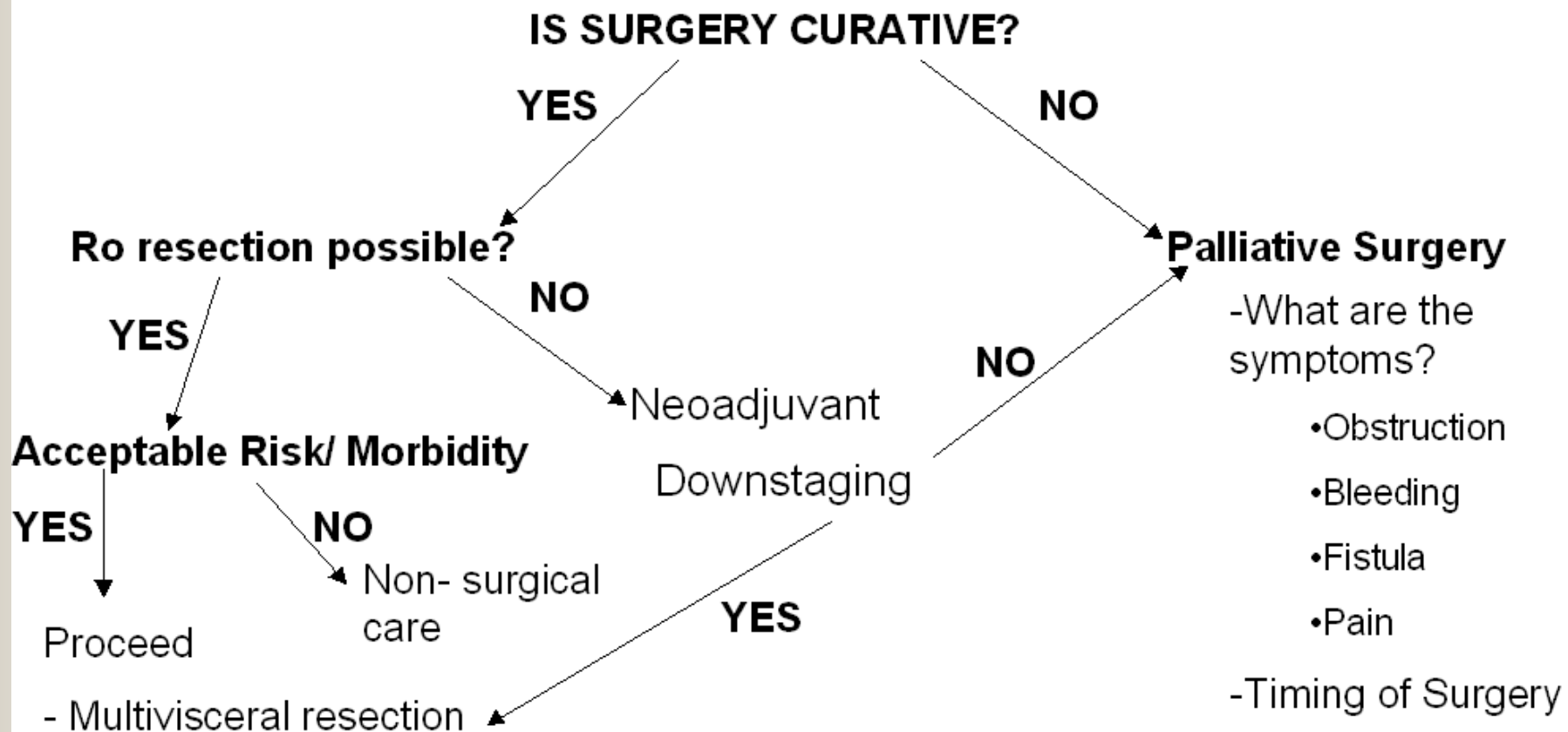


Common message

- Safe, feasible, equivalent operation
- Operative time longer
- Smaller incisions, less blood loss
- Postoperative recovery better
- But higher cost
- And more trials needed

Summary

Role Of Surgery in Advanced Colorectal Cancer





Conclusions

- It is impossible to palliate an asymptomatic patient
- It does not matter how much is removed but how much is left behind