



# The role of resection of the primary tumor in case of synchronous metastases?

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# Background

- Synchronous colorectal liver metastases (CLM) are seen in 20 to 25% of patients with newly diagnosed colorectal cancer (CRC)
- Only a minority are resectable
- Treatment strategy is a challenge to conciliate optimal treatment of the primary tumor and the metastase



# Prognostic value of synchronous presentation

- Some reports suggest a worse prognosis than for metachronous metastases
- Others not



## Treatment options for synchronous initially unresectable CRC liver metastases

- Up-front treatment is controversial
- Chemotherapy : which timing ? before or after surgery
- Surgery of the primary tumor +/- radiation or chemoradiation
- Surgery of the metastases if they become resectable



## **Up-front primary tumor resection in symptomatic patients**

- **In symptomatic patients (bleeding, obstruction, perforation) the primary tumor should be resected first.**
- **Alternatively: stoma, bypass, stent...**



## **Up-front primary tumor resection: non symptomatic patients**

- **Goals:**
  - avoid complications related to the primary tumor in place (bleeding, obstruction, tumor perforation) during chemotherapy particularly with bevacizumab.
  - cure (if metastases become resectable)
- **The majority of patients in the US used to undergo primary tumor resection**

**\* Chang et al, JCO 2012; Hapani et al, Lancet Oncol, 2009; Costi et al. Ann Surg Oncol 2007**



# Up-front primary tumor resection

- Up-front primary tumor resection delays administration of chemotherapy for several weeks.
- Complications of surgery can further delay or even preclude administration of chemotherapy.
- Complication rates for primary resection in patients with unresectable distant metastases was 11.8% (major complications) and 20.6% (minor complications) \*

\* Scheer et al. Ann Oncol 2008



# Up-front systemic chemotherapy

- Median survival of patients with unresectable metastases increased to more than 24 months with modern treatments.
- Systemic chemotherapy is active on liver metastases but also on the primary tumor and can even induce complete response in some cases .

Karoui et al. DCR, 2011; Schrag et al. JCO 2010; Grothey et al. JCO 2008;

*FOxTROT collaboration Group et al. Lancet 2012*





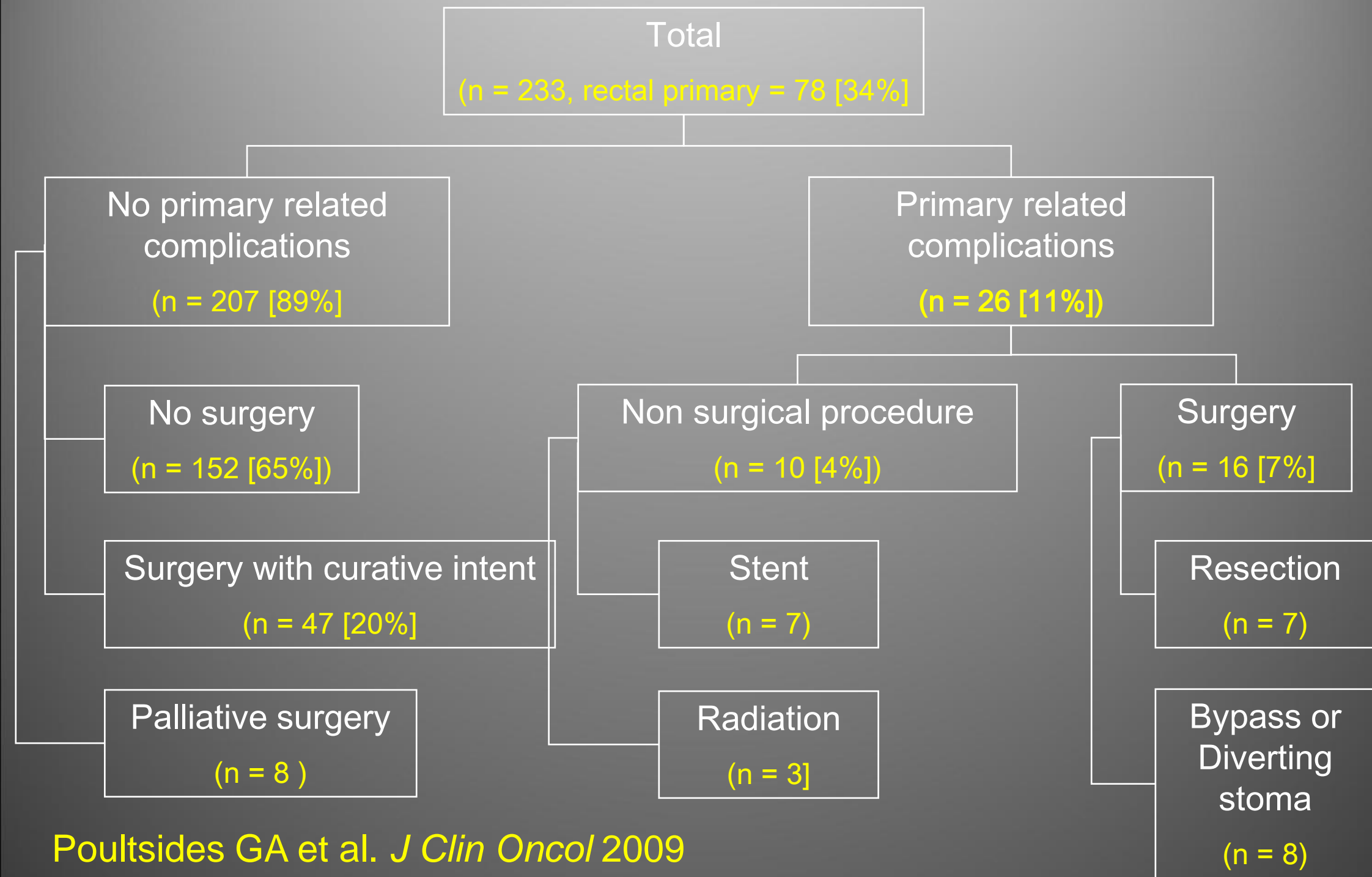
# Up-front systemic chemotherapy

- Retrospective studies have observed low rates of primary tumor–related complications during treatment in patients with initially asymptomatic disease. \*

\* Poultsides et al, JCO, 2009;



# Primary related complications and stage IV CRC treated by sytemic chemotherapy





**NSABP C-10:** ph. II prospective, single-arm study  
primary CT ( mFOLFOX6 + bev) for patients (n=86) with  
asymptomatic primary intact unresectable stage IV colon cancer

- The majority of patients could be managed without primary tumor (PT) intervention, (primary endpoint of the study )
  - 86% of patients had no major morbidity related to the intact PT
  - Median overall survival :19.9 months
- **The investigators conclude that avoiding resection of the asymptomatic PT did not result in an unacceptable rate of PT–related complications and did not compromise survival**
- 73.3% of the patients had not required PT resection at the time of death or last follow-up.



# Can primary tumor resection improve survival ?

- **Survival benefit suggested for patients with prior resection of primary**
  - Multi-institutional retrospective analysis \*
  - Population based studies \*\*, \*\*\*
  - Retrospective analysis of randomized trials \*\*\*\*, \*\*\*\*\*
- **These analysis are retrospective and potentially biased (patients selected for resection being better fit and with more limited metastatic disease)**
- **New prospective trials: CLIMAT-PRODIGE 30 ( France), CAIRO 4 (The Netherlands), SYNCHRONOUS ( Germany)**

\* Karoui et al. DCR, 2011; \*\* Gresham et al, Ann. Surg. Oncol.2014 ; \*\*\* Temple et al. JCO 2004; \*\*\*\* Ferrand F et al, Eur J Cancer 2013; \*\*\*\*\* Venderbosch et al, Ann. Surg. Oncol.2011



## **Need for resection of the intact primary after chemotherapy for synchronous metastases?**

- **Progression of metastases and asymptomatic primary: NO**
- **Tumor response: YES in particular if resection of metastases is considered**
- **Complete tumor response on primary tumor: discuss in MDM**



# **Chemotherapy can convert some patients with unresectable metastases to resection**

- **By intensified chemotherapy**
- **By combination of biologics and chemotherapy**



## **Surgical options if synchronous metastases become resectable after response to chemotherapy**

- **Resection of the primary tumor (+/- radiation or CRT for rectal cancer)**
- **Surgery of the liver**
- **Which order?**
  - **“Classical” primary tumor first?**
  - **Combined?**
  - **Reverse: liver first?**



## **Surgical strategy: the primary first**

- **Resection of primary tumor → Resection of metastases**
- **No risk of primary related complications**
- **Risk of progression of CLM which may become unresectable during the treatment of primary**





## **Surgical strategy: simultaneous resections of primary and metastases**

- **Advantages:**
  - Only one operation
  - Resection of metastases not delayed by the treatment of the primary
- **Limitations**
  - Increased morbidity (major liver resection + major colorectal surgery)
  - Requires double surgical expertise
  - Depends on surgical access ( open +/- laparoscopy)

Reddy et al. Ann Surg Oncol 2007, De Santibanes et al. J Am Coll Surg 2003, Fujita et al, Jpn J Clin Oncol 2000, Tocchi et al, Int J Colorectal Dis 2004; Adam et al.Br J Surg 2010



# Surgical Strategy: the combined approach

	Combined resection	Staged resection	P value
<b>Major Hepatectomy</b> n	36	51	
<b>Mortality</b> <b>Severe morbidity</b>	3 (8.3%) 13 (36.1%)	0 9 (17.6)	0.07 0.05
<b>Minor Hepatectomy</b> n	99	19	
<b>Mortality</b> <b>Severe morbidity</b>	1 (1%) 14 (14.1%)	0 2 (10.5%)	0.83 0.73



# Surgical Strategy: the combined approach

	Combined resection	Staged resection	P value
Major Hepatectomy			
Mortality	6.1%	2.4%	0.009
Minor Hepatectomy			
Mortality	2.2%	0.5%	0.11



# **Surgical Strategy: the reverse approach: liver surgery first**

- **Preoperative chemotherapy → Resection of metastases → Resection of the Primary Tumor**
- **Rationale:**
  - **Survival depends on progression of metastases rather than of the primary tumor**
  - **Prevents the risk of progression of CLM which could become unresectable during treatment of primary**
  - **Primary related complications during treatment of CLM are rare**



# **Surgery for synchronous colorectal liver metastases and primary: experience of M. D. Anderson**

<b>Approach</b>	<b>No Pts</b>	<b>Tumors No.</b>	<b>Mortality %</b>	<b>Cumulative Morbidity %</b>	<b>5y OS</b>
<b>Classic</b>	<b>72</b>	<b>3</b>	<b>3</b>	<b>51</b>	<b>48%</b>
<b>Combined</b>	<b>43</b>	<b>1</b>	<b>5</b>	<b>47</b>	<b>55%</b>
<b>Reverse</b>	<b>27</b>	<b>4</b>	<b>0</b>	<b>31</b>	<b>39%</b>
<b>P value</b>		<b>.01, .001</b>	<b>NS</b>	<b>NS</b>	<b>NS</b>

- **Provided adequate patient selection, the different approaches appear similar for postoperative morbidity and control of cancer**



# Cancer of the rectum and synchronous metastases

- No randomized trials
- Only retrospective series
  - A minority of patients with rectal cancer
  - Patients undergoing simultaneous resections had limited metastatic disease
- Treatment options depend on site and extent of primary tumor

Tanaka et al, Surgery 2004, Jaeck et al, Chirurgie 1999, Martin et al, J Am Coll Surg 2003, Chua et al, Dis Colon Rectum 2004



# Upper third or T2 rectal cancer

- No need for radiation
- Treatment strategy similar to colon cancer



# Locally advanced or low rectal cancer

## Objectives:

1. Control of rectal primary: integration of RT or CRT in the treatment strategy.
2. Control of liver metastases and avoid progression during treatment of primary.

## Limitations

- Chemoradiation
  - Provides suboptimal control of metastases during the 5 weeks of treatment.
  - Determines the date of surgery, 6 to 8 weeks after the end of radiation.
  - 5X5 Gy an alternative.
- Chemotherapy alone: suboptimal control of rectal primary.





# Conclusion

- No universal approach to synchronous CLM
- Treatment strategy:
  - Preoperative systemic chemotherapy
  - Surgical approach based on
    - ◆ Response to chemotherapy
    - ◆ Patient physical status (BMI, comorbidities,...)
    - ◆ Extent of primary tumor and metastases = treat the more threatening first
    - ◆ Operate site at higher risk of progression first