The Use of PET and PET/CT in the Management of Metastatic Colorectal Cancer

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Metastatic Colorectal Cancer

- Colorectal cancer (CRC) is the 3rd most common cancer worldwide and in the U.S.
- 3rd most common cause of cancer-related death for both U.S. men and women
- The liver and the lung are the most common sites of metastases
- 40-50% of patients will develop liver metastases during their disease course

The WHO. Cancer Fact Sheet No 297, 2013.
Nordlinger , et al. Lancet 2008
Vibert, Canedo, Adam. Semin Oncol 2005

Metastatic Colorectal Cancer

- Liver metastases are the most common cause of death
- Liver resection offers the possibility of long-term cure
- 20-30% of patients are ultimately able to undergo resection with resulting 5-year survival rates of 40-55%

Abdalla, et al. Annals of Surgery 2004
Mayo, et al. Surgery 2011

The Clinical Problem

- Patients with more than limited resectable extrahepatic metastases are not candidates for resection of liver mets
- Additional occult liver mets may also prevent curative resection
- A nontherapeutic laparotomy necessitates about 6 weeks off chemotherapy
- Potential for negative impact on quality of life

Research Question

Is there a role for PET or PET/CT in improving outcomes for patients with colorectal cancer liver metastases?

Existing Evidence

- A systematic review and 2 meta-analyses have failed to reach agreement on the imaging modality of choice (CT, MRI, PET or PET/CT) for detecting CRC metastases.

Patel et al., Ann Surg 2011
Niekel, Bipat, and Stoker, Radiology 2010
Mass, et al. Eur J Nucl Med Imaging 2011

RCT: Detection of Extrahepatic Disease

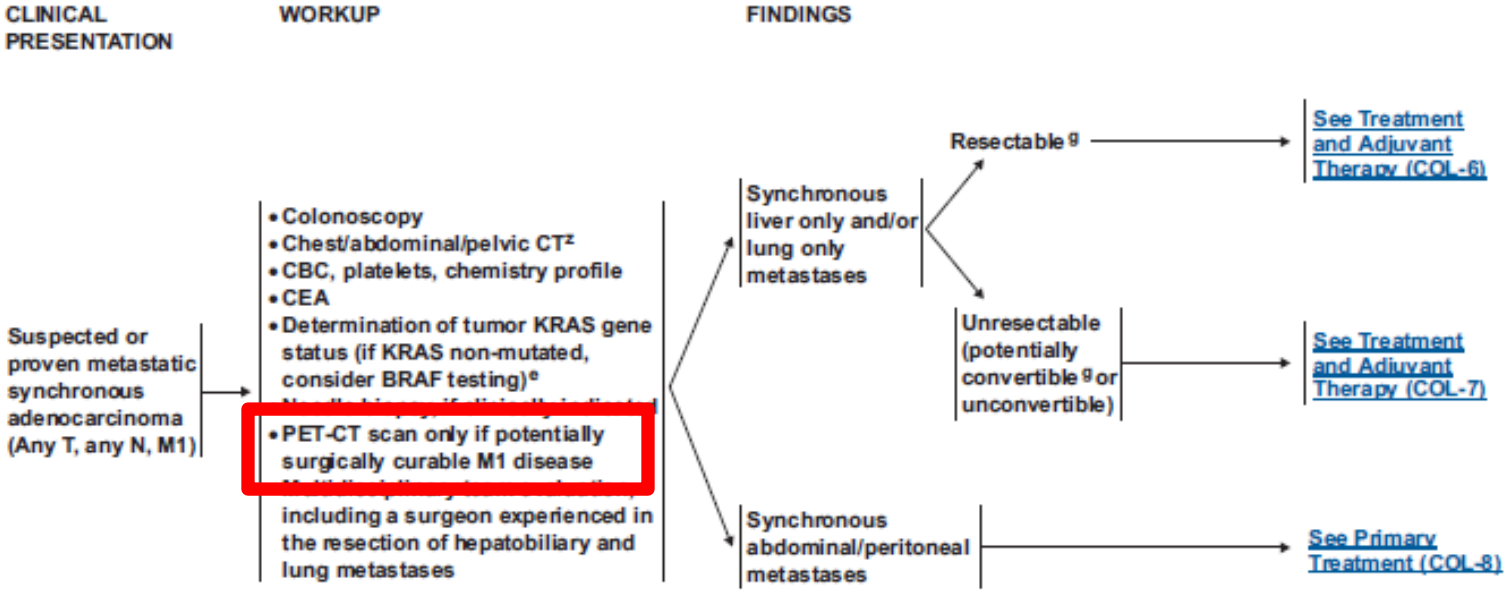
- CT-staged patients with potentially resectable CRC liver metastases: PET (not PET/CT) vs. no further imaging
- Disease recurrence within 6 months post-op was counted as "futile laparotomy"
- 38% RR reduction (95% CI 4-60%), 17% AR reduction in "futile laparotomy," NNT=6 with PET
- No significant difference in actuarial OS or DFS

Ruers, et al. J Nuc Med 2009

Limitations of PET/CT

- Detection threshold of 5 mm
- Low sensitivity in patients treated with neoadjuvant chemotherapy
- False positive rate?
  - Inflammation
- Cost – CT < MRI < PET

Patel, et al. Ann Surg 2011
Van Kessel, et al. Ann Surg Onc 2012



Synchronous Metastases

[e] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.
[g] See Principles of Surgery (COL-B 2 of 3).
[z] CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Colon Cancer

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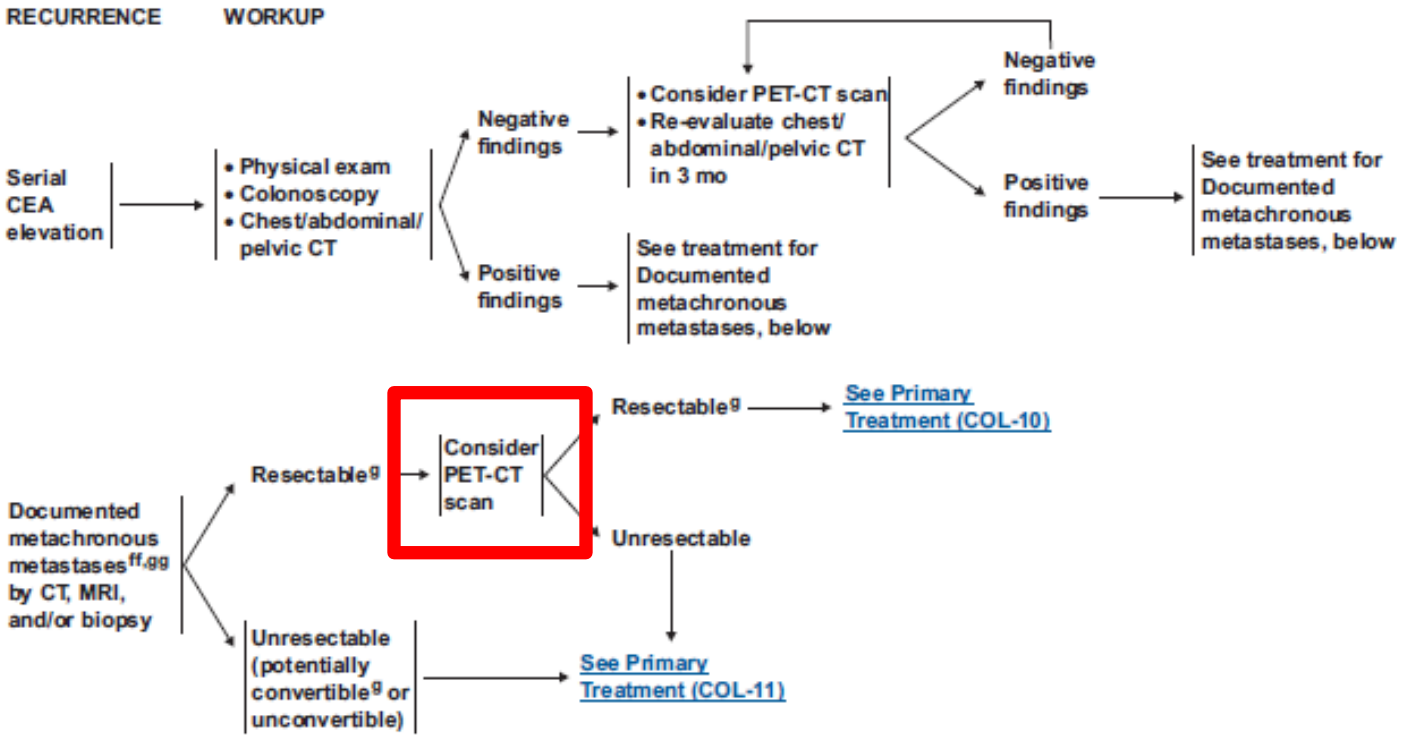
Colon Cancer Table of Contents
Discussion



Metachronous Metastases

[g] See Principles of Surgery (COL-B 2 of 3).
[ff] Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.
[gg] Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Clinical Relevance

- SEER-Medicare trends in PET use for CRC liver mets
  - 1996-2000=<2%, 2001-2002=<3%, 2003-2006=5.5%
- No known survival benefit
- Minimal benefit after chemotherapy
- Does avoidance of nontherapeutic laparotomy outweigh increased cost?

Mayo, et al. Surgery 2011

Study Aims

1. To identify trends in the use of PET and PET/CT in the management of patients with potentially resectable liver metastases from colorectal cancer
2. Evaluate the comparative effectiveness of PET/PET CT in the management of colorectal cancer metastatic to the liver

Aim 1

- To identify trends in the use of PET and PET/CT in the management of patients with potentially resectable liver metastases from colorectal cancer
  - Overall use
  - Use in patients receiving chemo

Cohort Selection

- TCR/SEER data from 2000-2009
  - Age ≥66
  - Colon or rectal cancer based on TCR site and ICD histology codes

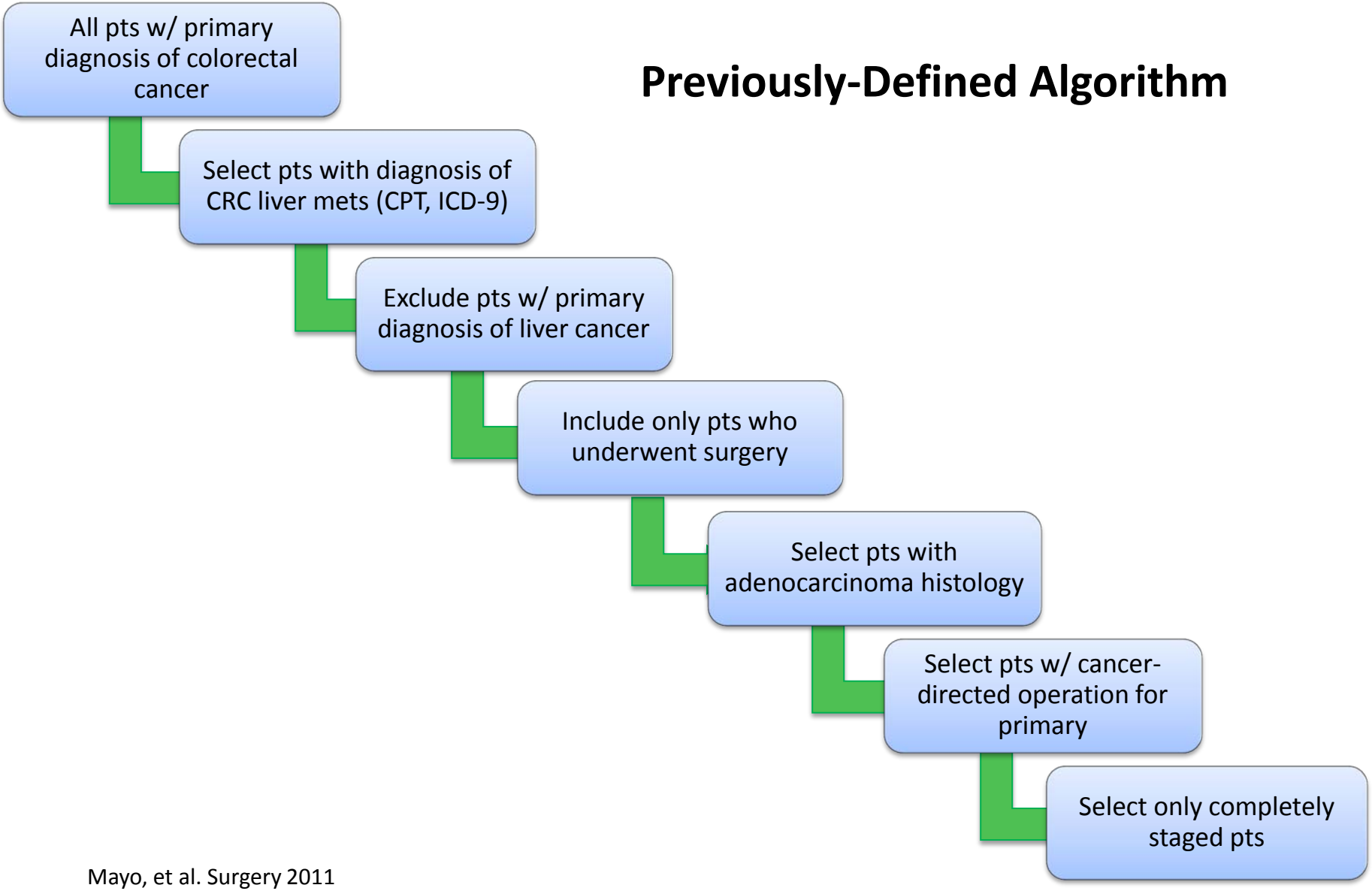
TCR site codes	ICD-9 codes
15=cecum	153.4
17=ascending colon	153.6
18=hepatic flexure	153.0
19=transverse colon	153.1
20=splenic flexure	153.7
21=descending colon	153.2
22=sigmoid colon	153.3
23=large intestine NOS	153.9
25=rectosigmoid junction	154.0
26=rectum	154.1

- ICD Histology codes
  - 8000-malignant neoplasm NOS
  - 8010-carcinoma NOS
  - 8140-adenocarcinoma NOS
  - 8141-scirrhous adenocarcinoma
  - 8143-superficial spreading adenocarcinoma
  - 8144-adenocarcinoma intestinal type
  - 8145-diffuse adenocarcinoma
  - 8210-adenocarcinoma in adenomatous polyp
  - 8211-tubular adenocarcinoma
  - 8220-adenocarcinoma in APC
  - 8221-adenocarcinoma in multiple adenomatous polyps
  - 8230-solid carcinoma NOS
  - 8260-papillary adenocarcinoma NOS
  - 8261-adenocarcinoma in a villous adenoma
  - 8262-villous adenocarcinoma
  - 8263-adenocarcinoma in tubulovillous adenoma
  - 8490-signet ring cell adenocarcinoma

Study Design

- Synchronous (simultaneous primary and metastatic disease) patients:
  - Code for colorectal adenocarcinoma
  - Code for stage IV disease
  - Code for liver metastases
- Metachronous (metastatic disease develops after treatment of the primary) patients:
  - Previously defined algorithm
    - Patients with prior diagnosis of colorectal cancer
    - Treatment with resection

Previously-Defined Algorithm



Mayo, et al. Surgery 2011

Study Design

- Synchronous disease
  - Time 0=day 15 of month/year of diagnosis

- Metachronous
  - Time 0=date of 1st code for liver metastases (197.7=secondary malignancy of liver) or liver resection

Cohort Selection (con't)

- Patients with synchronous or metachronous liver metastases from colorectal cancer from 2001-2009
  - Using claims 1 year before and 3 years after
  - Medicare part A&B 1 year before and 3 years after diagnosis or until death
- First cancer diagnosis
- Exclusions:
  - Unstaged disease
  - Carcinoma in situ
  - Anal cancers
  - Enrollment in Medicare for ESRD or chronic disability
  - Patients not living in Texas (TCR cohort) or in SEER regions (SEER cohort)

Population Demographic Characteristics

Characteristic	Synchronous	Metachronous
Gender		
Female	7889 (53.8%)	4443 (51.1%)
Male	6784 (46.2%)	4250 (48.9%)
Race/Ethnicity		
White	12156 (82.9%)	7293 (83.9%)
Black	1579 (10.8)	789 (9.1%)
Hispanic	293 (2.0%)	210 (2.4%)
Other	621 (4.2%)	391 (4.5%)
Unknown	24 (0.2%)	10 (0.1%)

Population Baseline Characteristics

Characteristic	Synchronous	Metachronous
Comorbidity Index		
0	8437 (57.5%)	4913 (56.5%)
1	3526 (24.0%)	2254 (25.9%)
2	1552 (10.6%)	914 (10.5%)
≥3	1158 (7.9%)	612 (7.0%)

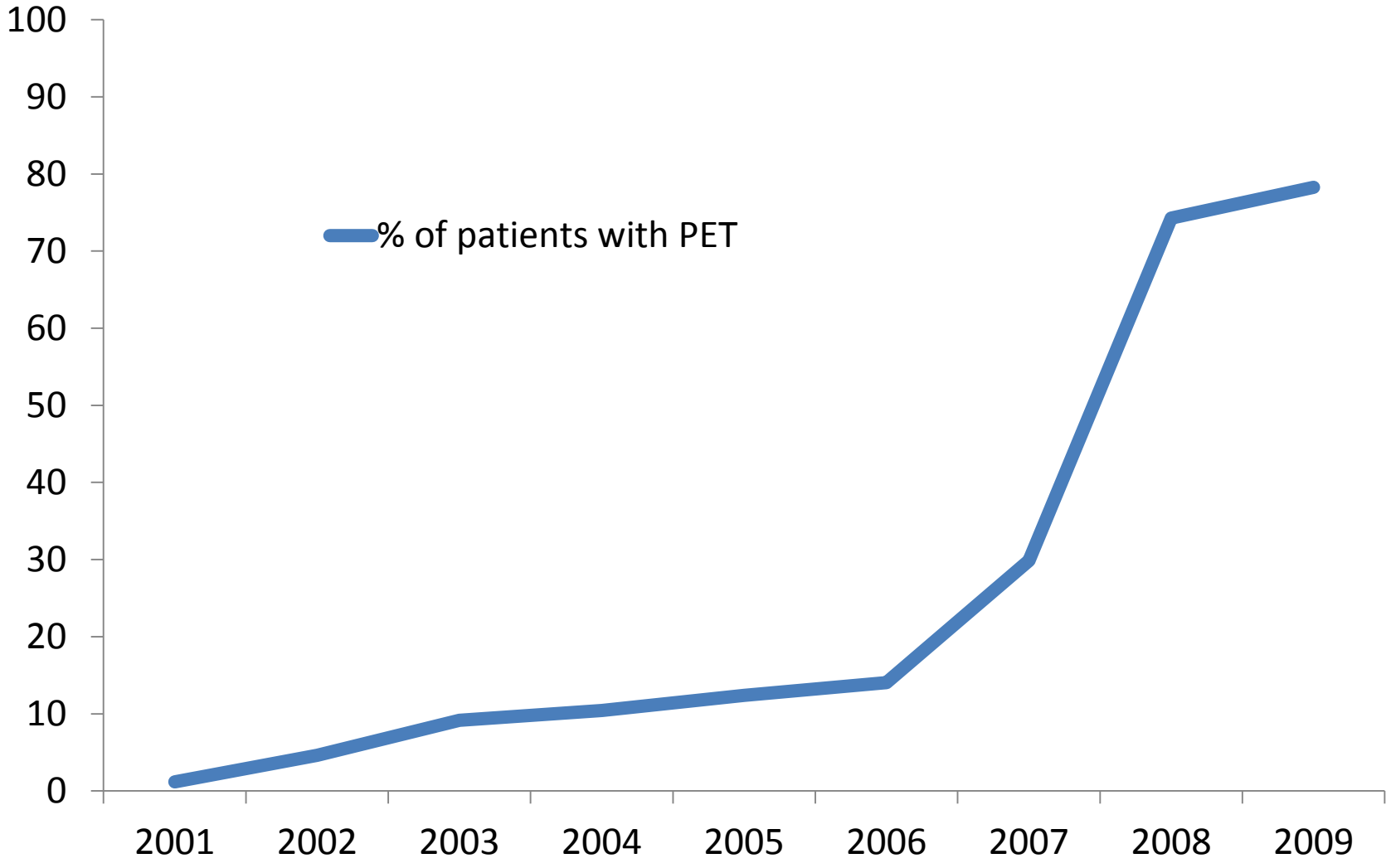
Population Tumor Characteristics

Characteristic	Synchronous	Metachronous
Site of Primary		
Colon	12250 (83.5%)	6944 (79.9%)
Rectum	2423 (16.5%)	1749 (20.1%)
Tumor Grade		
Well/moderately differentiated	7395 (50.4%)	6442 (74.1%)
Poorly differentiated	3552 (24.2%)	1829 (21.0%)
Undifferentiated	189 (1.3%)	73 (0.8%)
Unknown	3537 (24.1%)	349 (4.0%)
Stage (TCR)		
Local	0 (0%)	3030 (34.9%)
Regional	0 (0%)	5663 (65.1%)
Distant	14673 (100%)	0 (0%)

Analysis

- Time trends in use of any PET/PET CT
  - CPT PET
    - Limited area 78811
    - Skull base to mid-thigh 78812
    - Whole body 78813
  - PET/CT
    - Limited area 78814
    - Skull base to mid-thigh 78815
    - Whole body 78816
  - ICD-9: GI scan and radioisotope function study 92.04, Total body radioisotope scan 92.18

PET Use in Colorectal Cancer Liver Metastases by Year



Aim 2

- Evaluate the comparative effectiveness of PET/PET CT in the management of colorectal cancer metastatic to the liver

CE - Question 1

- Are rates of negative exploratory laparotomy different between patients with and without a preoperative PET/CT?
- Negative laparotomy
  - Exploratory laparotomy without liver resection or ablation
  - Were all done with the intent to resect liver mets?
  - Eliminate emergent exploratory laparotomy?

CE - Question 1

- Identify all patients with metastatic colorectal cancer who underwent
  - Exploratory laparotomy (alone)
  - Heptatectomy
  - Hepatic ablation (operative)
- Exclude patients with preoperative chemotherapy?

Laparotomy/Hepatectomy CPT codes

- Exploratory laparotomy: 49000 ICD-9: 54.1, 54.11
- Diagnostic laparoscopy: 49320, 49321, 49329; 54.21
- Liver biopsy, wedge: 47100 ICD-9: 50.12 (open), 50.19 (lap)
- Partial lobectomy/wedge: 47120 ICD-9: 50.22
- Trisegmentectomy: 47122
- Left lobectomy: 47125
- Right lobectomy: 47130
- Lobectomy (either or NOS): 47125, 47130 ICD-9: 50.3
- Unlisted laparoscopic liver procedure 47379

Hepatic Ablation

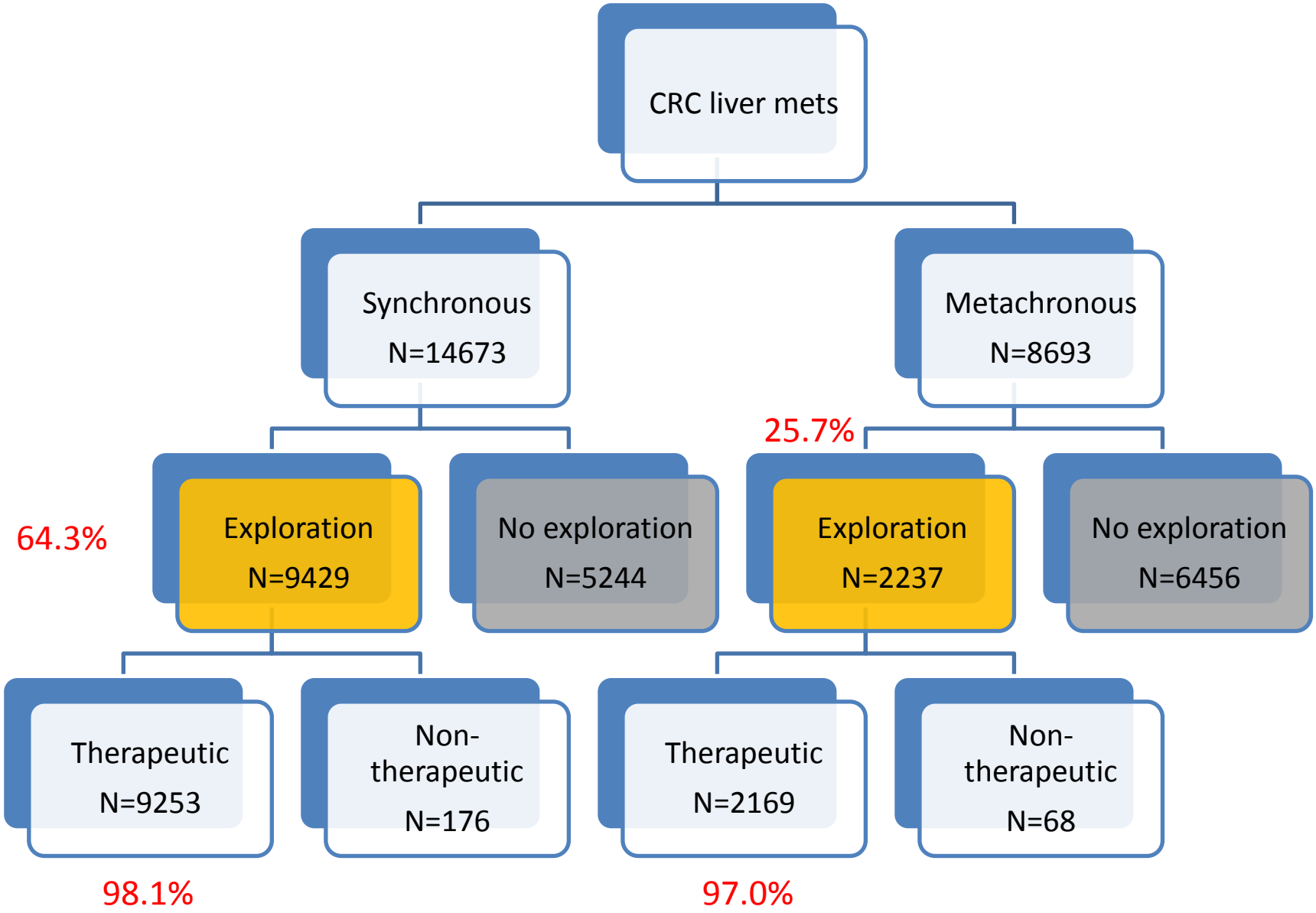
• Open		50.23
– Radiofrequency ablation (RFA)	47380	
– Cryosurgical	47381	
• Laparoscopic		50.25
– RFA	47370	
– Cryosurgical	47371	

Which Patients Underwent Exploration?

Explored	Synchronous	Metachronous
No	5244 (35.7%)	6456 (74.3%)
Yes	9429 (64.3%)	2237 (25.7%)
Therapeutic	9253 (98.1%)	2169 (97.0%)

Definition of Therapeutic Laparotomy

- Liver Resection
- Lymphadenectomy
- Bile Duct Excision
- Hepaticojejunostomy
- Hepatic Ablation
- Primary Colorectal Resection-synchronous disease only



Population Demographic Characteristics-Explored Patients

Characteristic	Synchronous	Metachronous
Gender		
Female	5088 (54.0%)	1150 (51.4%)
Male	4341 (46.0%)	1087 (48.6%)
Race/Ethnicity		
White	7913 (83.9%)	1909 (85.3%)
Black	893 (9.5%)	185 (8.3%)
Hispanic	193 (2.0%)	49 (2.2%)
Other	305 (3.2%)	91 (4.1%)
Unknown	15 (0.2%)	3 (0.1%)

Population Baseline Characteristics

Characteristic	Synchronous	Metachronous
Comorbidity Index		
0	5537 (58.7%)	1291 (57.7 %)
1	2321 (24.6%)	573 (25.6%)
2	946 (10.0%)	229 (10.2%)
≥3	625 (6.6%)	144 (6.4%)

Population Tumor Characteristics

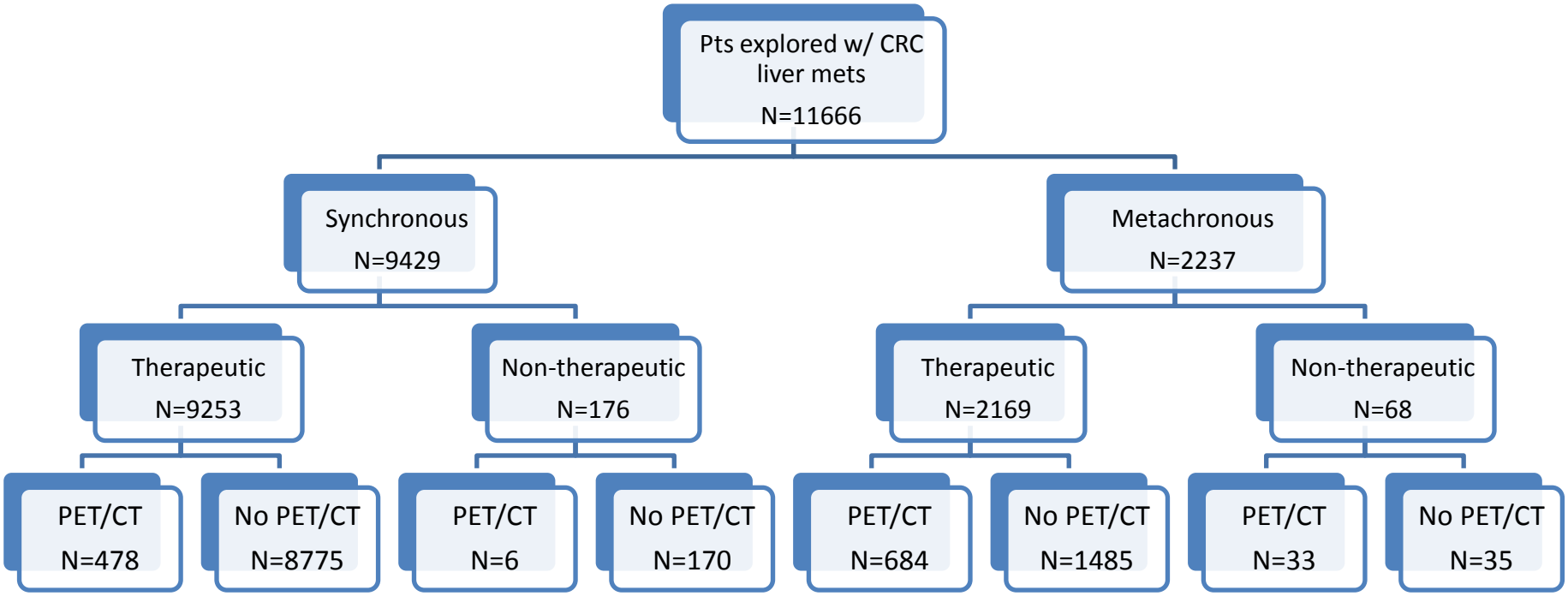
Characteristic	Synchronous	Metachronous
Site of Primary		
Colon	8060 (85.5%)	1864 (83.3%)
Rectum	1369 (14.5%)	373 (16.7%)
Tumor Grade		
Well/moderately differentiated	5690 (60.3%)	1691 (75.6%)
Poorly differentiated	2888 (30.6%)	442 (19.8%)
Undifferentiated	153 (1.6%)	21 (0.9%)
Unknown	698 (7.4%)	83 (3.7%)
Stage (TCR)		
Local	0 (0%)	812 (36.3%)
Regional	0 (0%)	1425 (63.7%)
Distant	9429 (100%)	0 (0%)

Imaging of Explored Patients

Imaging Study	Synchronous	Metachronous
CT/MRI/US	6315 (67.0%)	1074 (48.0%)

Why are so many patients missing imaging codes?

- Missing codes?
- Inappropriate time frame?
  - 3 months before or any time after diagnosis of mets, but prior to exploration
- Other suggestions?



5.2%

3.4%

31.5%

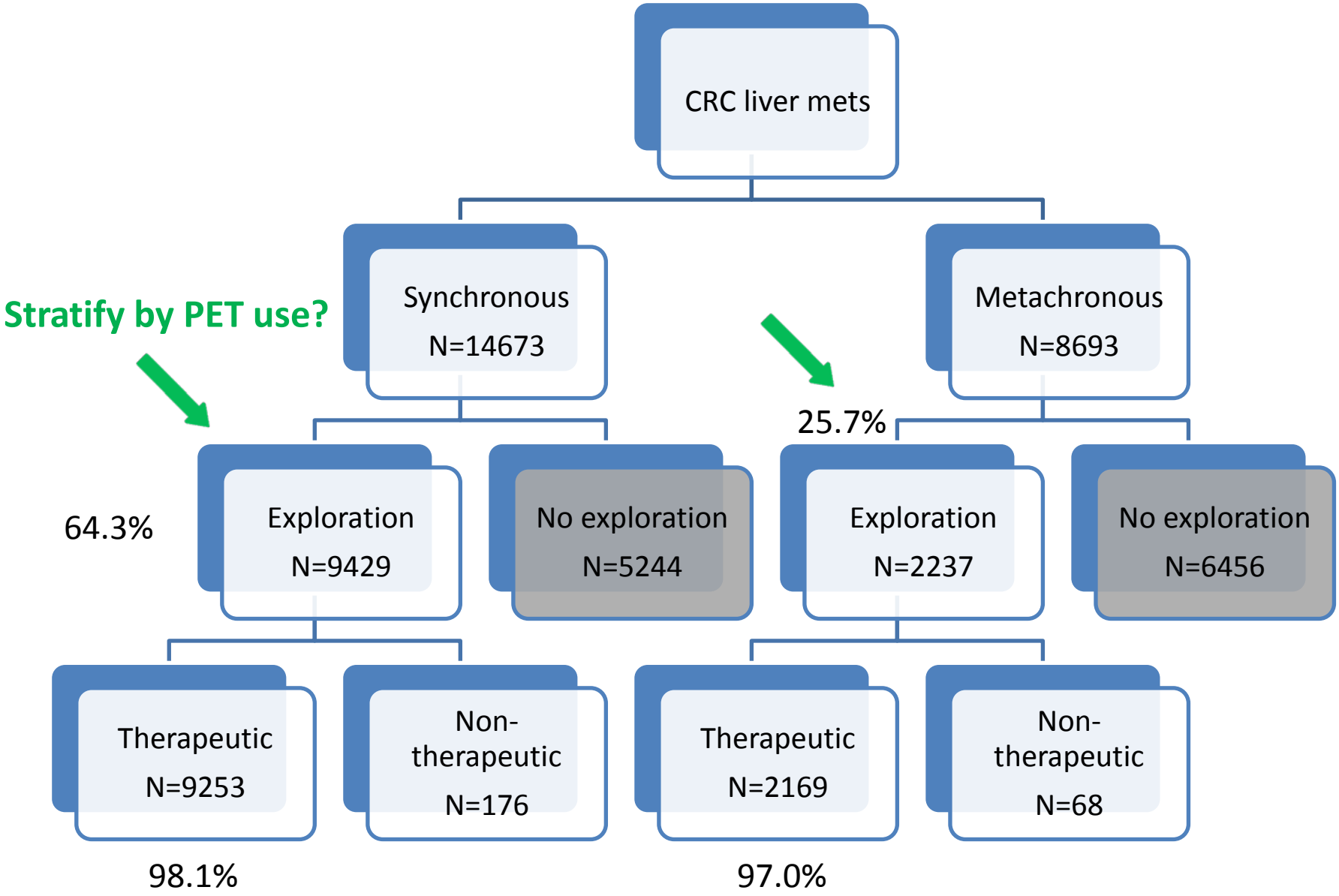
48.5%

In PET/CT group 98.8% of patients had a therapeutic laparotomy vs. 98.1% of patients without a PET/CT

In PET/CT group 95.4% of patients had a therapeutic laparotomy vs. 97.7% of patients without a PET/CT

CE – Question 2

- Are rates of ANY laparotomy (with or without liver resection) different for all patients presenting with metastatic disease with or without PET/PET CT?
- How would we do this?
  - Exclude patients with laparotomy + bowel resection unless liver resection is also done?
  - Comparison of laparotomy vs. laparoscopy rates?



Graph the trend of PET use with rates of exploration?

CE – Question 3

- Is survival better with or without PET/PET CT?
  - For overall cohort
    - Better selection of patients who will benefit from laparotomy and resection?
    - Potential reduction of time off chemotherapy for unresectable patients if nontherapeutic laparotomy is avoided
    - Potential to identify metastatic disease sooner → initiate chemo sooner

CE-Question 4

- Is PET/CT cost-effective for patients with liver metastases from CRC?
  - If there is a reduction in non-therapeutic laparotomy rates, does it offset the increased cost of PET?
  - What is the cost of any potential improvement in survival?

Study Limitations

- Inability to determine if operation was changed to a more extensive resection based on PET or PET/CT results
- Pre-test probability cannot be determined
- Are we actually answering our study question?

Other Potential Directions

- Trending the use of various imaging modalities over time: CT, MRI, and PET

- Looking at the cost associated with these trends

Questions?

Suggestions?