New Interventional Radiology Techniques in Bend: Minimally Invasive Cancer Therapy

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Personal Background

- Interventional Radiologist with Central Oregon Radiology Associates (CORA).
- Finished training June 2012 at the Dotter Interventional Institute at OHSU in Portland.
- Performed nearly 1000 cases there during my fellowship. Heavy emphasis on Interventional Oncology.
- No financial conflicts of interest to declare.

Interventional Radiology: What are we actually doing back there?

- Vascular: arterial and venous intervention (stents (peripheral, renal, visceral etc.), thrombolysis, ports, lines, dialysis access, etc.)
- Hepatobiliary: PTC, PBD, cholecystostomy, TIPS/DIPS, TJLbx, percutaneous G tubes, etc.
- Uro/gyn: percneph, ureteral stents, uterine artery embolization for fibroids, gonadal vein embo for varicocele or pelvic congestion syndrome.
- CT/US: biopsies and drainage.
- Acute: bleeder embolization (pelvic fractures, GI bleeds, splenic trauma, hemoptysis, etc.)
- Problem solving

...and now we treat cancer

- Interventional Oncology:
  - The treatment of cancer or cancer related problems using minimally invasive targeted treatments under imaging guidance.

Our Tools

- Catheter directed (intra-arterial) techniques:
  - Radioembolization, aka: Selective internal radiation therapy (SIRT, Y90)
  - Chemoembolization (chembo or TACE)

- Percutaneous techniques:
  - Radiofrequency ablation (RFA) and Cryoablation.

Which Cancers?

- Metastatic disease to the liver
  - Colorectal, neuroendocrine, breast, cholangiocarcinoma, GIST, melanoma, etc.

- Primary cancers of the liver and kidney
  - Hepatocellular Carcinoma (HCC)
  - Renal Cell Carcinoma
Presentation Outline

- Colorectal carcinoma
- Introduce radioembolization/Y90
- Hepatocellular carcinoma
- Introduce chemoembolization
- Cases

Metastatic Colorectal Carcinoma (mCRC)

Introduction to Y90

mCRC: US Epidemiology

- CRC is the third most common cancer diagnosed in the US
  - Estimated new cases in 2013:
    - Colon: 102,480
    - Rectal: 40,340
    - Median age at diagnosis: 69 yrs
  - Prevalence US, 2009 ~ 1.1 million
- CRC is the second leading cause of all cancer deaths
- 50,830 Estimated deaths in 2013

CRC and the liver

- 50-60% will develop liver metastases
  - 20% present with synchronous disease
  - 15-20% will develop metachronous liver mets within 3 yrs following resection of the primary tumor
- Liver metastases have the biggest impact on morbidity and mortality.
- Two thirds of mCRC patients die from their liver disease

Treatment Options

- Surgery
  - Only curable therapy.
  - Cytoreduction or Resection
    - 15-30% of patients present with resectable disease
    - 5 year survival
      - Resectable disease >50%
      - Unresectable disease <15%
      - Untreated, median survival of patients with mCRC is 6-8 months
  - Ablation (radiofrequency)– single / limited small lesions
    - Potentially curable

Majority of patients present with unresectable disease

- Options:
  - Chemotherapy.
  - Radiation therapy (external beam)
  - Catheter directed techniques (y90 and/or chemoembolization)
NCCN Guidelines: Chemotherapy agents recommended for unresectable mCRC

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Take away:
- Use of single agents improved median overall survival from <6 months to over a year.
- Combined agents and biologicals improved median overall survival to nearly 2 years.

Where does Interventional Radiology come in?

- This is evolving.
- Currently Y90 or chemoembolization is only used in patients with unresectable metastatic disease to the liver with evidence of disease progression on first line chemotherapy.
- Also known as “salvage” therapy.
- These are the sickest patients, having been through and ultimately failed multiple previous therapies.

St. Charles is the first center in Oregon outside of Portland to offer Y90 therapy!

Video

The Process

- Patients reach IR one of two ways:
  - Patients have established care in Bend, have progression of disease on chemotherapy, and are presented in our multidisciplinary tumor board.
  - Some patients will have been referred to or have sought care at OHSU. These patients are discussed in their liver specific tumor board. They then have the option to continue care at OHSU or closer to home here at St. Charles.
Benefits of local care

- Obviously less travel back and forth to Portland
- Clinic visits, imaging, and therapy which may require multiple overnight visits.
- We now offer the same therapies and the same or better quality of care as the larger academic institutions.

If it is determined that the patient is eligible, I will then see the patient in clinic (A radiologist with a clinic, what?).
- The patient’s imaging, labs, functional status, etc. are reviewed.
- The patient is then scheduled for the initial mapping arteriogram.

Mapping

Determining Shunt Fraction

- Dose is calculated (based on liver volume, tumor bulk, and lung shunt fraction).
- Dose is ordered.
- Patient returns for delivery of the radioactive beads. Usually around 2 weeks after the mapping arteriogram.

Therapy
**Therapy**

- Typically a day procedure.
- Similar experience for the patient as the mapping/embo procedure: arteriogram, dose delivery, and then a 4-6 hour recovery.
- Follow up visits as necessary, check LFT’s
- Ideally, follow up imaging should be performed at 3 months following therapy
  - Too soon, liver appears worse – inflammatory effect.

**Y90: safety**

- SIR-Spheres are FDA approved. Over 20,000 doses delivered since 2002.
- Radiation travels 2.5mm in tissue on average, no significant safety concerns on discharge.

**Y90: safety**

- Common adverse effects:
  - Fatigue: 6%
  - Nausea: 3%
  - Pain: 3%
  - Ascites: 0.5%
  - Fever
  - Transient elevation of LFT’s, peaks at 3-4 wks.

**Y90: Efficacy**

- Much of the clinical efficacy has been proven in the salvage setting, or patients with disease refractory to multiple rounds of chemotherapy.
  - This is reflected in the statistically significant but less than impressive numbers when it comes to reductions in time to progression or improvements in median survival.
  - Trends indicate that the quality of the outcome is directly related to the “quality” of the patient. For example: first line therapy, good liver function, good performance status. Very impressive overall response rates in this setting.
Limited data suggests significant improvement in survival when Y90 is used earlier and in combination with first line agents vs later in the treatment algorithm with sicker patients that have failed first line therapies.

More efficacy data is coming!

First-line treatment: PFS/TTP in prospective studies.

SIRFLOX

- Fully enrolled Level 1 randomized control trial for mCRC in the liver.
- Will examine the use of Y90 as first line therapy used in conjunction with FOLFOX chemotherapy.
- Multi-center, international study.
- Enrollment: Complete in April 2013 with 518 patients

Summary

- Y90
  - Provides an overall survival advantage to chemotherapy refractory patients
  - Increases response rates consistently across all lines of therapy
- Minimal Toxicities
  - Effective and safe in combination with many chemotherapy regimens
  - First line RCT fully enrolled
  - Outpatient procedure

Primary Hepatocellular Carcinoma (HCC)

Introduction to Chemoembolization

- 5th most common malignancy worldwide.
- Up to 500K deaths annually.
- Currently about 15K cases are diagnosed each year in the US.
- Median survival without treatment is dismal, approx. 6-8 months.
- Incidence in the US roughly doubled between 1975 and 1998. Rise is likely attributable to HCV. Continues to rise.
- Occurs in the setting of chronic liver disease. Usually viral hepatitis, ETOH induced liver disease, NASH, hemochromatosis, PBC, etc.
HCC

- Unlike other tumors that develop within a background of normal tissue, HCC occurs as part of a hepatic field change.
  - Replacement of liver parenchyma with fibrosis, scarring, and nodular regeneration
  - HCC results from a sequence of dedifferentiation:
    - Regenerative nodule – dysplastic nodule - HCC


HCC

- Changes to feeding vessels and neovascularization occur during the process.
- Overt HCC does not have a portal blood supply.
  - Supplied solely by abnormal, unpaired hepatic arteries.
  - Results in a characteristic vascular enhancement pattern used to make definitive radiologic diagnosis.


Diagnosis

- Almost entirely imaging based with biopsy reserved for lesions that do not exhibit typical imaging characteristics.

HCC: screening

- Several organizations (below) are now recommending screening ultrasounds and serum AFP in all pts with cirrhosis q 6-12 months.
  - American Association for the Study of Liver Disease,
  - United States Veterans Administration,
  - European Association for the Study of the Liver.
- May reduce HCC related mortality by 37%¹.

Zhang et al. J Cancer Res ClinOncol 2004; 130: 417-422

Staging

- The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely accepted staging system and is the recommended staging system as it combines prognosis prediction and treatment allocation.
- Based on patient’s performance status, Child-Pugh score (liver function), and tumor characteristics.
- These are the 3 factors shown to be independent predictors of survival.

BCLC: Staging/Prognosis/Therapy
Treatment: Early Stage

- Surgical resection is first line for patients with solitary tumors and preserved liver function
- Fewer than 10% of patients diagnosed with HCC are eligible.

Radiofrequency ablation is an excellent alternative for patients who are not surgical resection or transplant candidates.
- Results most favorable for tumors <3cm
- Complete sustained response in 97% of patients.
- 5 year survival nearly 70%
- Comparable to survival rates following surgical resection.
- Arguably an equivalent alternative to surgical resection as first line treatment.


For those not eligible for resection, Liver transplantation is considered first line.
- Pt must meet Milan Criteria (most commonly used)
  - Single tumor <5cm, or three tumors <3cm.

Treatment: Intermediate Stage

- Transarterialchemoembolization (TACE) is the recommended first-line therapy for intermediate-stage disease and is now considered the standard of care.
- Two landmark prospective RCT’s have demonstrated improved overall survival for TACE compared with BSC.

**Survival Benefit in TACE**

- Llovet Lo

National Cancer Study Group of Japan 2006

- Largest reported series of patients treated with TACE.
  - 8510 patients
  - Median survival was 34 months
  - 5 year survival was 26%
    - Compare to reported 5 year survival for surgical resection ranging 23-48%.

**Physiologic aspects of TACE**

- Hepatic tumors derive the majority of their blood supply from the hepatic artery, while normal liver parenchyma gets most from the portal vein.
- Allows for tumor specific delivery of chemotherapy without systemic toxic levels.
- Embolization of the supplying vessels induces tumor ischemia and restricts nutrients.
  - Ischemia may help overcome potential mechanisms of drug resistance by resulting in failure of cell membrane pumps leading to higher intracellular drug concentration.
  - “Dwell time” of chemotherapy is increased by the slowing of blood flow into and out of the tumor.

**Current Techniques**

- Chemotherapy, usually Doxorubicin or Epirubicin, is mixed with one of two embolic agents:
  - Lipiodol
    - Iodinated poppy seed oil.
    - Unique in that it is selectively taken up by hepatocytes.
    - “Stains” the tumor, making imaging follow up easier.
  - Porous drug-eluting microspheres. Proposed benefits include:
    - Slower release of the drug (12-14 days)
    - Lower systemic serum levels of the drug
    - Larger embolic particles better for highly shunting tumors or exophytic tumors which tend to hemorrhage more frequently.

**Technique**

- Very similar to Y90 delivery with catheters placed in the hepatic arteries via the groin.

**Periprocedural Care**

- First time TACE patients will be observed overnight.
- Repeat TACE patients usually go home same day.
# Periprocedural Care
- Post-embolization syndrome (pain, nausea/vomiting, fever, fatigue) is common and expected.
- Usually well tolerated with appropriate anticipatory supportive therapy.
- Patients receive zofran, dexamethasone, toradol, and an antibiotic (usually Cefotaxime) before and during the procedure.
- Narcotics during and after the procedure.
- Average hospital stay is 1.5 days.

# Y90 and HCC
- Early data shows possible benefit over TACE.
- Significantly improved toxicity profile for Y90.
- Currently reserved for large or infiltrative tumors in patients with relatively preserved liver function (total bili<2).

# TACE/Y90 and Transplant
- As it can take months to years to receive a liver transplant even if the patient is eligible, TACE and Y90 can serve as a “bridge” to transplantation by either stabilizing or reducing disease.
- Also, these catheter directed techniques can shrink tumors enough to make them eligible for transplant when they were not previously.

# Recommended Follow-up
- Multiphase CT or MRI one month after initial treatment.
- Then q 3 month the first year.
- Then q 6 months thereafter.

# At St. Charles
- 14 chemoembolizations
  - 3 patients returned to the ED within 3 days of the procedure with post embolic syndrome.
  - One major complication:
    - TACE related infarction of the left lateral segments of the liver (and tumors). Developed hepatic abscess requiring prolonged antibiotic course.
- 5 Y90 therapies so far. 3 more by year end.
  - No adverse effects/complications
  - Limited follow up data so far.

# Greatest Hits
HCC in right liver dome on MRI with hepatic venous invasion.

Preserved liver function.

Lesion not seen well on arteriography. Dose delivered using C-arm CT and careful review of prior imaging studies.

2 months post Y90. Actually looks worse.

6 months post Y90. “Radiation Segmentectomy”

Note the capsular retraction. No evidence of residual or recurrent disease.

Single large HCC with preserved liver function.

Hepatic Arteriogram
4.5 months post y90. Lesion is much smaller but there is residual disease.

TACE performed 6.5 months after Y90.

5 months after TACE (11 months after Y90)

Lesion is smaller and stained with Lipiodol. No evidence of residual or recurrent disease.

Metastatic neuroendocrine tumor

Patient had extra hepatic mets, but major morbidity was secondary to paraneoplastic syndrome (flushing, diarrhoea, etc) which is dependent upon hepatic metastatic disease.

Y90 to Right Hepatic Lobe

5 months post y90. No evidence of viable hepatic metastatic disease...and significantly improved symptoms!
Hepatic Arteriogram

Summary

- Interventional Oncologic techniques are safe, effective, and now available at St. Charles.