ORGANIZATION: **Los Angeles Radiological Society**
VENUE: **66th Annual Midwinter Radiology Conference**
DATE: **February 22-23, 2014**
TITLE: **Gastrointestinal Cancer Update: Esophageal Cancer, Rectal Cancer & SBRT for Liver and Pancreas Tumors**

Presenters:
Karyn A. Goodman, MD, MS – Associate Attending Radiation Oncologist, Memorial Sloan-Kettering Cancer Center

ANSWER KEY

QUESTION 1	DISCUSSION RE: ANSWER OPTIONS
In the Dutch CVKO 95-04 study of pre-operative short course RT followed by TME compared with TME alone for patients with T1-3 rectal cancer, the pre-operative patients experienced the following: A. Significantly reduced local recurrence with no significant increase in operative mortality B. Significantly reduced local recurrence with a significant increase in operative mortality C. No significant reduction in local recurrence with no significant increase in operative mortality D. No significant reduction in local recurrence with a significant increase in operative mortality	Correct answer: A. Significantly reduced local recurrence with no increase in operative mortality Explanation - see presentation, "New Paradigms in the Treatment of Rectal Cancer" slide 4, : There was a relative reduction of 50% in LR with pre-operative RT, from 11.1% to 5.1%, with operative mortality 4% vs. 3% in the pre-operative group.

REFERENCE FOR QUESTION 1

Peeters KC, Marijnen CA, Neqteqaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007; 246(5):693-701.

van Gijn W, Marijnen CA, Naqteqaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011; 12(6):575-82. Epub 2011 May 17

QUESTION 2	DISCUSSION RE: ANSWER OPTIONS
The study by Samuelian et al comparing concurrent 5FU and IMRT vs. conventional pre-operative pelvic irradiation for rectal cancer demonstrated: A. A significant decrease in the pathologic CR rate. B. A significant increase in the pathologic CR rate C. A significant increase in grade 2+ GI toxicity D. A significant decrease in grade 2+ GI toxicity	Correct answer: D. A significant decrease in grade 2+ GI toxicity Explanation: - see presentation, "New Paradigms in the Treatment of Rectal Cancer" slide 16: Grade 2+ GI toxicity was 48% with IMRT vs. 62% with CRT, p= .006, while pCR was 19% with IMRT vs. 28% with CRT, p=NS.

REFERENCES FOR QUESTION 2

Samuelian JM, Callister MD, Ashman JB, et al. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2012; 82(5):1981-7. Epub 2011 Apr 7.

Parekh A, Truong MT, Pachtan I, et al. Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer. Gastrointest Cancer Res. 2013; 6(5-6):137-43.

QUESTION 3	DISCUSSION RE: ANSWER OPTIONS
A test that is used to identify patients with poor-risk rectal cancer prior to treatment and in (some studies is preferred to endorectal ultrasound) is: A. PET B. MRI C. DRE by primary surgeon D. CT	Correct answer: B. MRI Explanation: - see presentation, "New Paradigms in the Treatment of Rectal Cancer" Slides #25, 26. While DRE is a very important part of the pre-treatment evaluation, its usefulness is more in determining whether the patient is a candidate for sphincter-sparing surgery. MRI and EUS are used to estimate the depth of invasion and detect suspicious lymph nodes.

REFERENCES FOR QUESTION 3

Mercury Study group, Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. Radiology. 2007; 243(1):132-9. Epub 2007 Feb 28

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QUESTION 4	DISCUSSION RE: ANSWER OPTIONS
For esophageal cancer the MUNICON-1, MUNICON-2, CALGB 80803 and MSKCC trials evaluating post-treatment change in metabolic activity as a predictor of outcomes such as pCR and , what cutoff SUV decline was used to define PET-responders? A. > or = 25% B. > or = 35% C. > or = 50% D. > or = 75%	Correct answer: B. > or = 35% Explanation – see presentation, "Directing Therapy for Esophageal Cancer: The Emerging Role of Imaging as a Biomarker and Guide for RT Delivery" Slides 17, 18, 21 22 and 24

REFERENCE FOR QUESTION 4

Weber WA, Ott K, Becker K, Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2001; 19:3058-65

Ott K, Weber WA, Lordik F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol. 2006;24(29):4692-8. Epub 2006 Sep 11

Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007; 8(9):797-805

QUESTION 5	DISCUSSION RE: ANSWER OPTIONS
Residual mesorectal lymph node involvement following neoadjuvant combined modality therapy for rectal cancer in the MSKCC series for patients with a primary pCR (ypT0) was: A. <10% B. 10-19% C. 20-29% D. 30-39%	Correct answer: A. 7 Explanation - see presentation, "New Paradigms in the Treatment of Rectal Cancer" Slide 48 from the series referred to in the lecture. The overall incidence of positive MLN involvement was 27%, and incidence paralleled pathologic T stage (pT): pT0 = 7%, pT1 = 8%, pT2 = 22%, pT3 = 37%, and pT4 = 67%. The point was that primary tumor response is not always predictive of lymph node response, which is a potential counter-argument to non-operative management.

REFERENCE FOR QUESTION 5

Stipa F, Zernecke A, Moore HG et al. Residual mesorectal lymph node involvement following neoadjuvant combined-modality therapy: rationale for radical resection? Ann Surg Oncol. 2004; 11(2):187-91.

Pucciarelli S, Capirci C, Emanuele U, et al. Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. Ann Surg Oncol. 2005; 12(2):111-6. Epub 2005 Feb 4

QUESTION 6	DISCUSSION RE: ANSWER OPTIONS
Which of the following has NOT been demonstrated for pre-operative chemoradiation for locally advanced rectal cancer? A. It is associated with an improvement in risk of local recurrence. B. It allows for sphincter preservation C. It is associated with an improvement in overall survival D. It is associated with less sphincter dysfunction over baseline.	Correct answer: C. It is associated with an improvement in overall survival Explanation - see presentation, "New Paradigms in the Treatment of Rectal Cancer" Slides 6, 19-20, 65. While pre-operative chemoradiation has been associated with reduced local recurrence and improved sphincter preservation, it has been associated with increased sphincter dysfunction over baseline, and survival has not been shown to be improved.

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REFERENCE FOR QUESTION 6

Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731-40

Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. J Clin Oncol. 2010; 28(27):4233-9. Epub 2010 Jun 28.

QUESTION 7	DISCUSSION RE: ANSWER OPTIONS
Excessive dose of radiation to the liver can cause radiation-induced liver disease (RILD) which is characterized by all of the following except: a. Fatigue b. Ascites c. Melena d. Elevated liver enzymes e. Hepatomegaly	ANSWER: C. Explanation: See Presentation, "SBRT for Liver and Pancreas Malignancies: slide 2. Liver is very sensitive to excessive doses of radiation to a large volume. Is important for treating physician to be able to recognize and understand clinical symptoms associated with RILD, which include fatigue, ascites, elevated liver enzymes and an enlarged liver (hepatomegaly.) Melana is NOT a characteristic of this condition.

REFERENCES FOR QUESTION 7

Tefft M, Mitus A, Das L, et al. Irradiation of the liver in children: review of experience in the acute and chronic phases and in the intact normal and partially resected. Am J Roentgenol. 1970' 108:365-385.

Reed GB Jr., Cox AJ Jr: The human liver after radiation injury. A form of veno-occlusive diseas. Am J Pathol. 1966;48:597-611.

QUESTION 8	DISCUSSION RE: ANSWER OPTIONS
Stereotactic Body Radiation Therapy (SBRT) for liver tumors: a. Has been associated with duodenal ulcers when single fraction SBRT has been delivered to lesions in the porta hepatis. b. Has been shown to provide > 90% local control at 2 years in phase 1 / 2 study when giving 36-60 Gray in 3 fractions. c. When given in 5 fractions, has resulted in a higher response rate and 2 year local control when 60 Gray was given versus 30 Gray. d. Is felt to be safe and feasible for Child Pugh Class A, but not Child Pugh Class B patients. e. All of the above.	ANSWER: E. Explanation: See Presentation, "SBRT for Liver and Pancreas Malignancies: slides 13, 17, 19, and 33. Studies in the literature have provided clinicians a wealth of information on the proper use of SBRT for liver tumors. Giving a high single dose of SBRT to certain areas of the liver (ie. porta hepatis) has been found to result in an increased risk of causing a duodenal ulcer. Rusthoven, et al reported on phase I / II study that when given 3 fractions, ranging from 36-60 Gray, to liver tumors he was able to show a 92 % local control rate at 2 years and 100 % local control rate when lesions were less than or equal to 3 cm. Rule, et al. reported results of Phase I / II study at UT Southwestern that revealed increased response rates with dose escalation using 5 fractions (60 Gray better 2 year local control than 30 Gray.) When given in 5 fractions, SBRT has been shown to be more effective when the cumulative dose is 60 Gray versus 30 Gray. Child Pugh Class B patients are NOT good candidates for SBRT.

REFERENCE FOR QUESTION 8

Goodman KA, Wiegner EA, Maturen KE, et al. Dose Escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. Int J Radiat Oncol Biol Phys. 2010; Oct 1; 78(2): 486-93.

Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I / II trial of stereotactic body radiation therapy

ANSWER KEY

for liver metastases. J Clin Oncol. 2009 Apr 1;27(10): 1572-8.

Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol 2011 Apr; 18(4): 1081-7.

Lasky FD, ASTRO 2012. Slide 33.

QUESTION 9	DISCUSSION RE: ANSWER OPTIONS
Which of the following strategies has NOT been used to improve targeting of abdominal tumors? a. Abdominal compression b. Placement of fiducial markers c. Conebeam CT scans d. Vac Loc bags e. Biological Mesh Spacers	ANSWER: D. Explanation: See Presentation, "SBRT for Liver and Pancreas Malignancies: slides 40, 41, 42, 43, 44 and 45. Abdominal compression, placement of fiducial markers, conebeam CT scans and Permanent spacers (ie. Biological mesh spacers) have been used to improve targeting of tumors in the abdomen. VacLoc bags have not been used regularly for this function.

REFERENCE FOR QUESTION 9

Pishvaian AC, Collins B, Gagnon G, et al. EUS-guided placement for Cyberknife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc. 2006 Sept; 64(3):412-7.

Eccles CL, Patel R, Simenov AK, Lockwood G, et al. Comparison of liver tumor motion with and without abdominal compression using cine-magnetic resonance imaging. Int J Radiat Biol Phys. 2011 Feb 1; 79(2): 602-8.

QUESTION 10	DISCUSSION RE: ANSWER OPTIONS
Studies with SBRT for pancreatic tumors has revealed the following except: a. Increased toxicity when given as a boost after 45 Gray IMRT with concurrent 5FU. b. Dose to duodenum needs to be minimized to decrease patient's chance of developing a duodenal ulcer. c. Induction gemcitabine followed by 3 fraction SBRT between cycles 3 and 4 resulted in 85% local control, but 9% had late grade 3 toxicites. d. Phase 2 multi-institutional study of SBRT for unresectable pancreatic cancer during which SBRT (6.6 Gy x 5 fractions) was given after 1 cycle of Gemcitabine and before a subsequent cycle found that tumors in the body and tail of the pancreas had a higher median overall survival than those involving the head of the pancreas. e. None of the above.	ANSWER: D. Explanation: See Presentation, "SBRT for Liver and Pancreas Malignancies: slides 58, 66, 69, 70,and 76. Koong, et al found in a Phase II study of SBRT boost that giving 45 Gy IMRT with concurrent 5 FU followed by a SBRT boost was associated with increased acute GI toxicity. Murphy has shown that the volume of the duodenum to which a certain dose of radiation corresponds with likelihood of developing Grade 2-4 duodenal toxicity. Mahadevan looked at treating patients with induction gemcitabine followed by 3 fraction SBRT between cycles 3 and 4 and reported 85% local control, but some late grade 3 toxicities. Dr. Goodman reported results of phase II multi-institutional study of Stereotactic Body Radiation Therapy for Unresectable Pancreatic Cancer looking which showed that patients with tumor located in head of pancreas had a nearly statistically significant increased overall median overall survival versus those with lesions in the body or tail of the pancreas.

REFERENCE FOR QUESTION 10

Koong AC, Christofferson E, Le QT, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advance pancreatic cancer. Int J Radiat Oncol Biol Phys. 2005 Oct 1;63(2):320-3.

Murphy JD, Christman-Skieller C, Kim J, et al. A dosimetric model of duodenal toxicity after stereotactic boyd radiotherapy for pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010 Dec 1;78(5):1420-6.

Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):e615-22.