■ Sat-389 ■

The predicting pathologic complete response about neoadjuvant chemoradiotherapy in esophageal cancer

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Background/Aims: Neoadjuvant chemoradiation (nCRT) followed by surgery is the preferred treatment for locally advanced ESCC. But a recent trial suggested close observation might be a reasonable option in patients achieving clinical complete response (CR) to nCRT. For this strategy, accurate clinical assessment for predicting pathologic CR (pCR) is essential. In NCCN guidelines PET/CT is recommended as response assessment, whereas endoscopy is optional after nCRT. **Methods:** In 222 patients who received nCRT (40–59.6Gy) plus surgery for locally advanced ESCC at Asan Medical Center from 2007 to 2014, the performance of endoscopy and PET/CT which were done 4-8 weeks after nCRT for predicting pCR was evaluated. Metabolic CR (mCR) was defined as complete resolution of FDG uptake within all lesions, making them indistinguishable from surrounding tissue, and endoscopic CR (eCR) as no residual mucosal lesions except for scar change. **Results:** pCR (ypT0N0) was achieved in 102 patients (46.0%), and ypT0N+ in 17 (7.7%). Among patients who underwent PET/CT (n=220), mCR was obtained in 97 (44.1%), and non-mCR in 76 (34.5%), whereas metabolic response could not be assessed due to diffuse esophagitis in 47 (21.4%). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mCR for pCR was 57.0%, 45.8%, 58.8%, and 72.4%, respectively. Among patients who underwent endoscopy (n=218), eCR was obtained in 40 (18.3%), and the sensitivity, specificity, PPV, and NPV of eCR for pCR only in primary tumor site (ypT0N+/-) was 29.9%, 95.1%, 87.5%, and 53.9%, respectively. When adding endoscopic response to metabolic response, the sensitivity, specificity, PPV, and NPV of clinical CR for pCR was 28.3%, 94.0%, 80.0%, and 60.8%, respectively, and the positive likelihood ratio for pCR was 4.8 (95% CI 2.2–10.6). (Table 1) **Conclusions:** The addition of endoscopic evaluation to metabolic response after nCRT improved specificity and PPV for pCR compared to metabolic response alone, which could help in applying surveillance strategy without immediate surgery in patients achieving clinical CR after nCRT for ESCC.

Table 1: Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of CT-PET and Endoscopic Assessment Post-nCRT to Predict pCR

	Sensitivity		Specificity		Positive predictive value		Negative predictive value		Positive likelihood ratio		Negative likelihood ratio	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI		95% CI		95% CI
mCR*[a]	57.0%	46.7-66.9%	45.8%	36.7-55.2%	58.8%	40.9-52.6%	72.4%	48.7-63.3%	1.05	0.83-1.33	0.94	0.70-1.26
eCR**[b]	29.9%	21.8-39.1%	95.1%	88.8-98.4%	87.5%	74.0-94.5%	53.9%	50.8-57.1%	6.04	2.46-14.84	0.74	0.65-0.84
cCR***	28.3%	19.7-38.2%	94.0%	88.1-97.6%	80.0%	64.6-89.8%	60.8%	57.6-63.9%	4.73	2.16-10.35	0.76	0.67-0.87

* mCR indicated metabolic complete response; ** eCR, endoscopic completes response; *** cCR, clinical complete response

[a] Intention-to-diagnose principle, non-evaluable results were considered as false negative when calculating sensitivity and as false positive when calculating specificity.

[b] Pathologic complete response was defined as no residual tumor cell in the primary site only.

■ Sat-390 ■

Jejunum polyp in patient treated with BRAF inhibitor, Vemurafenib

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Background: BRAF inhibitors(BRAFi) extend survival in BRAF-mutant melanoma, but paradoxical activation of the mitogen-activated protein kinase(MAPK) pathway increases the risk of developing gastric polyps and colonic polyps. To our knowledge this is the first report of detecting jejunum polyp in melanoma patient who was treated with BRAFi. **Case presentation:** A 64-year-old male diagnosed primary nodular melanoma on right medial side of tibia without ulcer in August 2010. He underwent a wide local excision without adjuvant therapy. New skin lesion appeared on right lateral thigh, and surgical excision with split thickness skin graft was performed, followed by radiotherapy in March, 2011. However, he was presented with local recurrence with metastasis to several lymph nodes, liver, and left adrenal gland in November, 2016. The pathology of skin lesion revealed BRAFV600E mutation. He had received 960 mg of vemurafenib twice daily since December, 2016, and achieved partial remission until January, 2018. However, follow-up study detected intraluminal polypoid mass at proximal jejunum with residual metastatic mass in left adrenal gland, liver in April, 2018. Small bowel endoscopy was performed, and 3cm-sized polypoid mass was confirmed. He underwent diagnostic laparoscopic small bowel segmental resection in June, 2018, and pathological examination of jejunum polyp demonstrated high grade dysplasia adenoma. At the same time, he got metastasectomy which were left adrenalectomy and hepatic segmentectomy. Histology of liver showed metastatic melanoma, and adrenal gland showed residual degenerated melanoma cells. **Conclusion:** Previous reports have revealed that BRAFi for treating melanoma promote the progression of intestinal polyp. This goes along with our finding that the patient treated with vemurafenib was found to have jejunum polyp, even though small bowel is known to be a rare site for neoplasia. Surveillance endoscopy should be considered for patients treated with BRAF inhibitors. This finding could support the combination with BRFAi and MAPKi to advanced BRAFV600 mutated melanoma decreases MAPK-driven acquired resistance and paradoxical MAPK pathway activation.

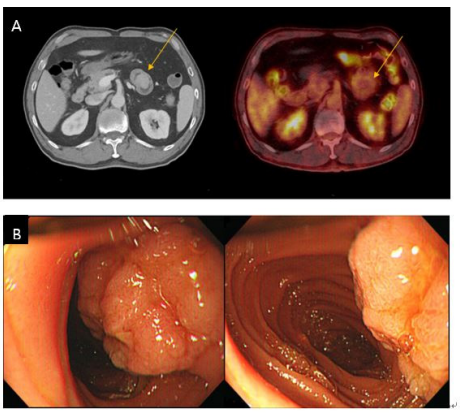

Figure 1. (A) Cross sectional image of a FDG PET/CT obtained from a BRAF mutant melanoma patient with Vemurafenib after 2 years of therapy. The intense uptake of radiotracer in a jejunum (arrow) (B) Representative small bowel endoscopy which demonstrated a 30mm jejunum tubular adenoma