

LETTERS TO THE EDITOR

Mutational status of lung cancer patients and survival outcomes for patients with limited brain metastases

Dear Editor,

The high-quality phase III trial JCOG0504 by Kayama and colleagues made important contributions to literature and our clinical perspective [1]. This randomized, prospective study demonstrated the noninferiority of surgery with salvage stereotactic radiosurgery (STS) to surgery with whole-brain radiation therapy (WBRT) in patients with one to four brain metastases. The median overall survival (OS) which is the primary end point of the study was 15.6 months in both WBRT (n=137) and salvage STS arms (n=134), respectively (HR:1.05, noninferiority margin ≤ 1.385 , $p=0.027$). The study population has different types of tumors (lung, breast, colon etc.) and the leading primary site was non-small cell lung cancer (NSCLC) for both groups with rates of 48.2% and 47% respectively (n=66 and 63). May be, the clinicians will have a chance to know the effects of STS and WBRT on survival in NSCLC subgroup as well as other primary sites. Moreover, as a part of the highly heterogeneous NSCLC spectrum, the prognostic effects of EGFR or ALK mutations on outcomes may be considered for two different treatment arms.

In NSCLC, activating mutations of EGFR and ALK are present in approximately 10-15% and 5% of patients, respectively. In a fashion similar to JCOG0504, in East Asian population EGFR mutations may present up to 60% of lung adenocarcinoma patients [2]. The EGFR or ALK mutant NSCLC patients tend to have a higher brain metastases rate because of prolonged survival with targeted therapies [3]. Also, recent data showed that mutant EGFR but targeted therapy-naive stage I-III patients may have a higher tendency to develop brain metastases on their follow-up compared with wild-type NSCLC patients. In the JCOG0504 study, 21.2% of the WBRT arm and 26.1% of the STS arm received any kind of targeted therapy for all cancer types. But the proportion of the NSCLC patients who received targeted therapy in different arms is not known.

In the JCOG0504 study there was a substantial increase in survival in many types of cancer after the targeted therapies had started to use. The median OS of the WBRT and STS arms were 15.1 vs 13.8 months in the 2006-2010 enrollment period and 16.3 vs 17.3 months in the 2011-2014 enrollment period. The EGFR or ALK mutations of the brain metastatic NSCLC had the most dramatic results of this era. Wild-type NSCLC with ≥ 4 brain metastases had worse outcomes compared to single or limited (≤ 3) brain metastases. In contrast, in the study of Cleveland Clinic Neuro-Oncology Center, the median OS of the brain metastatic ALK or EGFR mutant patients was significantly

longer compared to wild-type NSCLC patients (19.9 vs. 9.8 months). Furthermore, in the mutant group, the number of brain metastasis had not effect on OS, unlike wild-type NSCLC. In the mutation-positive group with 1, 2-3 and >3 brain metastasis the median OS was 16.7, 19.1 and 23.7 months respectively [4]. In another retrospective analysis, EGFR mutant and tyrosine kinase inhibitor (TKI) treatment-naive NSCLC patients with brain metastasis, STS, WBRT or upfront TKI therapy had a statistically significant difference in median OS with 46, 30 and 25 months, respectively [5]. From this point of view, we believe that it will be beneficial to know the percentage of ALK and EGFR mutant NSCLC patients in the treatment arms and the effects of WBRT or STS treatments on survival in these subgroups.

References

1. Kayama T, Sato S, Sakurada K et al. Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. *J Clin Oncol*, 2018; p. JCO2018786186.
2. Li C, Fang R, Sun Y et al. Spectrum of oncogenic driver mutations in lung adenocarcinomas from East Asian never smokers. *PLoS One* 2011;6:e28204.
3. Eichler AF, Chung E, Kodack DP et al. The biology of brain metastases-translation to new therapies. *Nat Rev Clin Oncol* 2011;8:344-56.
4. Balasubramanian SK, Venuz VA, Chao ST et al. Impact of EGFR and ALK mutation on the outcomes of non-small cell lung cancer (NSCLC) patients with brain metastases. *J Clin Oncol* 2016;34:(Suppl abstr 2005), 2016. 2016 ASCO Annual Meeting.
5. Magnuson WJ, Lester-Coll NH, Wu AJ et al. Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naive Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. *J Clin Oncol* 2017;35:1070-7.

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Can we rely on body mass index when predicting post-operative outcomes and survival of esophageal cancer patients?

Dear Editor,

We read with great interest the meta-analysis entitled: 'Impact of high body mass index on surgical outcomes and long-term survival among patients undergoing esophagectomy' [1]. The authors conducted a systematic review and meta-analysis to investigate the relationship between high body mass index (BMI), postoperative outcomes and prognosis in cancer patients undergoing esophagectomy. According to the results, high BMI was significantly associated with increased rate of wound infection, cardiovascular complications and anastomotic leak, whereas a lower incidence of chylous leakage was observed. Moreover, in a subgroup analysis, high BMI was associated with a better overall survival (OS) of patients undergoing esophagectomy.

Nonetheless, BMI cannot adequately distinguish the different types of obesity, especially in terms of adiposity and muscle mass. The effects of BMI on postoperative complications and OS might be better attributed to patients' body composition. More specifically, visceral fat is considered to be the culprit that leads to the metabolic and clinical consequences of obesity, due to the secretion of a number of adipokines, cytokines, and growth factors. Saeed et al. demonstrated that visceral adiposity, assessed through CT scans, seems to be a better indicator of OS and disease free survival in esophageal cancer patients undergoing esophagectomy [2].

Furthermore, current research supports that sarcopenic patients have impaired OS, while are more susceptible to developing complications after an invasive and time-consuming operation, such as esophagectomy. A good illustration of these points can be found in the results of a recent meta-analysis that showed a positive association between sarcopenia and postoperative pulmonary complications after esophagectomy, whereas a negative association between sarcopenia and survival was observed [3]. In addition, sarcopenic obesity is an important factor that predisposes esophageal cancer patients to develop dose-limiting toxicity during neo-adjuvant chemotherapy [4]. Nevertheless, little is known about the impact of sarcopenic obesity on postoperative outcomes in esophageal cancer patients, indicating an interesting factor to shed light on.

Last but not least, the preponderance of esophageal cancer patients experience preoperative unintentional weight loss (WL), mainly due to dysphagia symptoms.

Therefore, WL may be a better predictive factor for OS, given that unintentional preoperative WL of $\geq 10\%$ before esophageal cancer resection was related to worse 5-year OS [5], while malnourished patients could be still classified as obese according to BMI.

Conclusively, BMI does not provide a good insight into patients' body composition, thus obfuscating the results. Preoperative WL, sarcopenia, sarcopenic obesity and visceral adiposity may be more accurate in defining obese and malnourished patients, rather than the absolute BMI values.

References

1. Gao H, Feng H-M, Li B et al. Impact of high body mass index on surgical outcomes and long-term survival among patients undergoing esophagectomy: A meta-analysis. *Medicine (Baltimore)* 2018;97(28):e11091.
2. Saeed N, Shridhar R, Almhanna K, Hoffe S, Chuong M, Meredith K. CT-based assessment of visceral adiposity and outcomes for esophageal adenocarcinoma. *J Gastrointest Oncol* 2017;8:833-41.
3. Boshier PR, Heneghan R, Markar SR, Baracos VE, Low DE. Assessment of body composition and sarcopenia in patients with esophageal cancer: a systematic review and meta-analysis. *Dis esophagus* 2018. doi:<https://dx.doi.org/10.1093/dote/doy047>.
4. Anandavadivelan P, Brismar TB, Nilsson M, Johar AM, Martin L. Sarcopenic obesity: A probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clin Nutr* 2016;35:724-30.
5. van der Schaaf MK, Tilanus HW, van Lanschot JJB et al. The influence of preoperative weight loss on the postoperative course after esophageal cancer resection. *J Thorac Cardiovasc Surg* 2014;147:490-5.

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