Editorial

Does the "obesity paradox" really exist in lung cancer surgery?—maybe we should recognize what is the "obesity" first

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Although there are many other measures for subject body composition, the body mass index (BMI), calculated by the total weight divided by the square of height, has been widely accepted as a universal tool for the patient health risk assessment. A dramatic increase in baseline BMI has been reported to show a definitive correlation to a range of metabolic, cardiovascular, and malignant diseases (1,2). Current evidence demonstrates that the patients with BMI ≥30 kg/m^2, who are generally considered as the 'obese' patients in routine clinical practice, may have both significantly higher morbidity and mortality rates after elective surgery, especially after cardiac operations (3,4). However, it seems that such "obese" patients may have a lower mortality rate after lung cancer surgery (3).

In the latest evidenced-based review conducted by our research team, we synthesized the outcome data from 25 eligible cohort studies and further identified a paradoxical benefit of the "obesity" (defined by BMI ≥30 kg/m^2) for overall morbidity, in-hospital mortality and long-term survival in patients undergoing lung cancer surgery (5). The favorable effects of per unit increase in BMI and the obesity defined by BMI ≥30 kg/m^2 were also supported by the most recent large-scale single-center retrospective analysis conducted by Dr. Boris Sepesi with his colleagues from the University of Texas MD Anderson Cancer Center (6). In Dr. Sepesi's study, the authors reviewed the survival data of 1,935 surgical patients with non-small cell lung cancer (NSCLC) during a 15-year period and found:

(I) Per unit increase in BMI remained an independent prognostic factor for overall survival (OS) in both univariable (P<0.01) and multivariable (P=0.02) Cox regression analyses;

(II) "Morbidly obese" patients (BMI ≥35 kg/m^2) had a tendency towards better OS than that of "obese" patients (BMI ≥30 but <35 kg/m^2: P=0.05), overweight patients (BMI ≥25 but <30 kg/m^2: P=0.13) and normally weight patients (BMI ≥18.5 but <25 kg/m^2: P=0.37);

(III) Propensity score matching analysis demonstrated that the patients with BMI ≥30 kg/m^2 had a significantly better OS than that of patients with BMI ranged 18.5–25 kg/m^2.

Dr. Sepesi with his colleagues further analyzed the available data from The Cancer Genome Atlas (TCGA) dataset and sought to investigate the genetic connection behind the association between a high level of BMI and improved OS of NSCLC. The authors found that the overexpression of uncoupling protein 2 (UCP2), a member of the mitochondrial uncoupling protein family with the function to suppress the production of mitochondrial reactive oxygen species, promote the fatty acid oxidation and limit the utilization of glycolysis-induced pyruvate, was

significantly associated with better postoperative OS (6,7). This TCGA dataset analysis might support the most recent laboratory evidence indicating that the upregulation of UCP2 might play a key role to inhibit the proliferation of cancer cells by regulating the cellular metabolism (8).

Both of above findings from current high-quality investigations seem to support that the "obesity paradox", a new phenomenon showing favorable and protective effects of the clinically diagnosed obesity (BMI ≥30 kg/m^2), may really exist in lung cancer surgery (5,6,9). We have tried to explain the possible reasons underlying the "obesity paradox" in our systematic review with meta-analysis (5). We hypothesized that these "obese" patients with operable NSCLC might have a younger age and more peripheral adipose tissue, receive a more regular and intensive medical treatment, and own a better ability to store nutrients to resist surgical interventions compared with the normal/underweight patients (5). Although there is some truth in all of these possible mechanisms, they still remain speculative.

However, Dr. Katherine Flegal with her colleague recently recommended that we should abandon the application of the term "obesity paradox" since the term "obesity paradox" was a figure of speech, not a scientific term with a precise definition (10). Dr. Flegal thinks that the "obesity paradox" terminology is essentially a rhetorical device in which the researchers collect a range of current studies together and further identify a unitary phenomenon showing an unexpected benefit of clinically diagnosed obesity (BMI ≥30 kg/m^2). Such findings can be easily influenced by a variety of confounding factors that may differ across diseases and treatments, and are not necessarily mutually exclusive, such as the selection bias from the retrospective nature (11), undetected cachexia (12), weight loss induced by chronic wasting diseases before surgery (13), and lower likelihood of receiving guideline-recommended treatments (14). The "obesity paradox" terminology oversimplifies a complex of underlying pathophysiological mechanisms. Dr. Flegal further indicates that more worrying is the misleading information conveyed by clinical investigations stating the concept of the "obesity paradox" to the general public (10). Therefore, the simplest way to avoid the wrong message to general population, which suggests that "the obesity may be favorable", is just to describe the patterns of association between different levels of BMI and clinical outcomes rather than to inculcate the term "obesity paradox" in the future (10).

In our systematic review, we had ever hypothesized one plausible reason indicating that being obese might not be protective but being underweight had a significant relationship with worse postoperative outcomes (5). In Dr. Sepesi's study, the authors carried out a propensity score matching analysis based on 464 well-matched pairs of surgical patients, and then compared the OS between two groups of patients with BMI <25 kg/m^2 (normal/underweight) and with BMI ≥25 kg/m^2 (overweight/obese). They found that the patients with BMI <25 kg/m^2 had a significantly worse prognosis than that of patients with BMI ≥30 kg/m^2 (obese) and with BMI ≥35 kg/m^2 (morbidly obese). Furthermore, the patients with BMI <18.5 kg/m^2 (underweight) seemed to have similar outcomes to those of patients with BMI ranged 20–25 kg/m^2 (normal). To our knowledge, abundant evidence demonstrates that the underweight state defined by BMI <18.5 kg/m^2, which can represent a seriously declined nutritional reserve, serves as a potent prognostic factor for poor surgical outcomes (15-17). As we previously reported, these findings may create an illusion that the "obesity" state, which is generally identified by BMI ≥30 kg/m^2, has a paradoxical benefit in surgical populations (5). We tend to agree with Dr. Flegal's opinions suggesting that it may be more appropriate to study the "normal weight paradox", instead of the "obesity paradox", to find why normal weight isn't associated with favorable survival in surgical populations (10).

The major concern that urges us to re-examine the "obesity paradox" in lung cancer surgery is the measurement of "obesity". Essentially, obesity is a body composition disorder defined by relative or absolute excess of body fat (18). Abundant evidence demonstrates that excess adiposity is characterized by a deteriorated physiological state due to alterations in the insulin metabolism (insulin resistance), sexual hormone levels, activation of growth factor signaling, induction of special lipids, and secretion of inflammatory cytokines, such as the tumor necrosis factor-α and interleukin-6 (19-21). Evidence from the latest molecular studies also support that excess adiposity plays a pivotal role in controlling cellular growth, proliferation and cancer progression by activating the mammalian target of rapamycin (mTOR) pathway, and in regulating essential metabolic processes through reactive oxygen species (22). Therefore, the obesity-induced metabolic disruptions can contribute to create a favorable environment for tumorigenesis and cancer progression (23). Given such concerns, it will be easily understood that the "obesity" state, which follows the nature of "an excess of body fat", is hypothesized to worse the prognosis after a cancer diagnosis.

However, in the majority of current epidemiological studies and clinical trials, the baseline BMI, an objective, simple and convenient method, is still utilized as the most common surrogate measure for obesity (24). Actually, BMI usually fails to provide accurate information on subject body composition due to its major limitation in distinguishing between lean body mass (including skeletal muscle, organs, bone, and connective tissue) and fat body mass (25). Evidence from imaging reports indicates that there can be substantial variation in the amount and distribution between muscular tissue and adipose tissue among cancer patients with identical BMIs (26). The performance of BMI to diagnose excess adiposity has a high specificity but really low sensitivity, resulting in the failure of accurate obesity detection (27). Applying BMI alone may overestimate the "obesity" in the individuals with abundant muscular mass or with volume overload, but conversely, underestimate the "obesity" in the elderly people and the cancer patients who tend to suffer from progressive wasting of lean body mass as well as abundance of adiposity due to malignant behaviors (27-29). This major limitation also makes the BMI fail to provide a sufficient sensitivity to measure the adiposity across ethnically diverse populations among whom there is profound variation in body composition (26,27).

Another imperfection of BMI as a surrogate measure for excess adiposity is that BMI fails to differentiate the regional distribution of fat (26,30). It has been recognized that the susceptibility to suffer from obesity-induced metabolic complications is not essentially mediated by total body fat mass, but is strongly dependent on the body fat distribution and the ability of subcutaneous adipose tissue to sufficiently expand when necessary (30-33). The validity of BMI to identify the "obese" patients will be largely attenuated since BMI cannot satisfy the physicians to distinguish between adipose tissue components (i.e., visceral, subcutaneous, intermuscular, and intramuscular) (26).

Given above limitations of BMI for measuring obesity or distinguishing between diverse body composition components, we suggest that it may be more reasonable to regard BMI as a rough proxy to assess lean body mass, because the baseline BMI itself mainly reflects total body weight rather than fat body weight, and the lean body mass takes up approximately 75–90% of total body weight in normal adults. On the contrary, regarding BMI as a proxy for adiposity has a great probability of exposure misclassification, resulting in a large decline of evidence power for associations with clinical outcomes (27). Therefore, we recommend thoracic surgeons to utilize the clinically routine computed tomography scans or other effective biomedical imaging methods (i.e., dual-energy X-ray absorptiometry and bioelectrical impedance analysis), rather than just to calculate the simple BMI, to provide precise estimates of both muscle and adipose tissues, because the precise quantification of fat body mass and lean body mass has broad implications for personalized cancer care, including the tailored lifestyle interventions, risk stratification for surgery and neoadjuvant/adjuvant chemotherapy dosing (26,34,35).

Given above reviews, we finally advocate what Dr. Cespedes with her colleagues recently recommended that it may be more appropriate to use the term "BMI paradox", instead of the term "obesity paradox", to indicate the better survival outcomes in the cancer patients with a higher level of BMI (26). It will be extremely important to recognize whether "a higher BMI" or "excess adiposity" is protective or harmful for malignancy prognosis first. Then, on the basis of accurate assessment of body composition, we will be able to develop the evidence-based guidelines and further design appropriate therapeutic options to promote the health and longevity of cancer survivors (26).

In summary, we think that we need to recognize which patients should be considered as "obese" first when discussing whether the "obesity paradox" really exists in lung cancer surgery. The "obesity" defined by BMI alone may fail to provide a precise estimate of body fat mass due to major limitations of BMI for distinguishing between body composition components and for differentiating body fat distribution. We should not deny that a higher level of BMI may be significantly associated with more favorable survival of operable NSCLC. However, the potential of "obesity paradox" in lung cancer surgery needs to be re-examined through the independent prognostic significance of both adipose and muscular tissues rather than of the BMI only.

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Footnote

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