Editorial Commentary

Substantial imbalance that is never eliminated with propensity score matched analyses in comparing surgery to stereotactic body radiotherapy for patients with early-stage non-small cell lung cancer

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Currently, lobar resection is the standard of care for medically operable patients with early-stage non-small cell lung cancer (NSCLC), while stereotactic body radiotherapy (SBRT) is preferred for patients deemed medically inoperable and those who wish to avoid surgery (1). However, it has not yet been established and remains controversial whether surgical resection or SBRT is superior for high-risk, operable patients. Many comparative studies, including propensity score matching (PSM) analysis and meta-analyses collecting PSM data (*Table 1*), have been reported, with inconsistent results.

Until recently, meta-analysis data suggested that overall survival (OS) following surgery was superior to that following SBRT. However, no significant differences in cancer-specific survival (CSS) were demonstrated. Recently, Cao *et al.* (2) reported a systematic review and meta-analysis that included one of the greatest numbers of eligible studies and patients among all meta-analyses conducted thus far. To confirm the validity of each study, these investigators evaluated several known variables for each PSM study. Variables were divided into three categories: patient characteristics, preoperative risk factors, and tumor characteristics. The results indicated that surgery was superior to SBRT with respect to clinical outcomes, including OS and CSS, in both matched and unmatched cohorts, while SBRT was associated with fewer perioperative deaths.

Although preoperative risk factors included comorbidities, disability index, performance status, and pulmonary function tests, these cannot adequately estimate preoperative risks because these covariates were not necessarily evaluated in all the studies. Therefore, these studies failed to diminish the impact of the substantial confounding of medical operability. In addition to the meta-analysis by Cao *et al.*, all the meta-analyses that used PSM consequently compared "medically operable patients treated with surgery" with "medically inoperable patients treated with SBRT" in a general manner. In fact, approximately 70% of matched patients treated with SBRT were deemed medically inoperable in one of the comparative studies (10). Such imbalance will not only affect OS but also CSS and disease-free survival (DFS). For example, frail patients regarded as inoperable would be less likely to receive various therapies at recurrence and/or have less physical and immunological capacity to cope with cancer, which could also affect these outcomes.

Two possible sources of substantial imbalance exist with respect to tumor characteristics. One is stage migration,

Table 1 Hazard ratios or odds ratios in meta-analyses comparing surgery and SBRT

Author	Year	Surgery	OS				CSS				DFS			
			Studies (n)	Patients (n)	HR (OR)	95% CI	Studies (n)	Patients (n)	HR (OR)	95% CI	Studies (n)	Patients (n)	HR (OR)	95% CI
Cao (2)	2018	Surgery	14	17,888	(1.71)#	1.52–1.93	8	1,722	(1.78)#	1.28–2.48	7		(1.83)#	1.06–3.16
		Lobectomy	8		(1.61)#	1.23–3.12								
Chen (3)	2018	Surgery	15	19,882	1.48#	1.26–1.72	8	4,020	1.17	0.92–1.50				
		Lobectomy	9	5,412	1.61#	1.27–2.03	4	934	1.35	0.70–2.62				
		Sublobar	6	12,568	1.28#	1.06–1.56	4	2,972	1.22	0.95–1.57				
Wang (4)	2018	Surgery	7	928	(0.98*)	0.53–1.82	3		(1.20*)	0.33–4.36	5		(1.48*)	0.85–2.54
			7		(2.11**)#	1.55–2.86	3		(1.94**)#	1.05–3.57	5		(1.63**)#	1.12–2.36
			1		(2.40***)#	1.71–3.36	3		(1.32***)	0.81–2.14	3		(1.42***)	0.94–2.15
Wang (5)	2017	Sublobar	4	917	(1.63*)	0.65–4.09								
			5	1,016	(2.17**)#	1.21–3.87								
			3	693	(3.55***)#	1.06–11.94								
Wen (6)	2017		9		1.59#	1.29–1.88					3		1.58	0.87–2.85
Yu (7)	2017		11		2.22#	1.97–2.50					5		2.37#	1.99–2.82
Zheng (8)	2014	Lobectomy			0.52	0.20–1.36							2.26	0.36–14.14
		Limited resection			0.49	0.19-1.30							2.92	0.50–16.97
Zhang (9)	2014		6	432	(1.31*)	0.90–1.91	2	175	(1.00*)	0.42–2.38	2	133	(1.11*)	0.59–2.10
			6	432	(1.82**)#	1.38–2.40	2	175	(1.31**)	0.81–2.12			(1.19*)	0.71–1.99

OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; CI, confidence interval. *, 1-year; **, 3-year; ***, 5-year; #, statistically significant.

Table 2 Summary of studies used in the analysis of CSS and DFS by Cao *et al.*

Author	Speciality	Year	Data	N (all, surgery/SBRT)	N (matched, surgery/SBRT)	Size	Staging (surgery/SBRT)	Location	Histology	PET
Paul (12)	T.S	2017	SEER	2,253/2,967	643/643	O	Path/clin	–	O	O
Shirvani (13)	R.O.	2014	SEER	1,496/382	251/251	O	Path/clin	–	–	O
Boyer (14)	R.O.	2017	VACCR	8,428/3,012	193/193	–	Clin/clin	–	O	–
Robinson (15)	R.O.	2013	Single	260/78	76/76	–	Clin/clin	–	–	–
Cornwell (10)	T.S	2018	Single	127/56	37/37	–	–	–	–	–
Miyazaki (16)	T.S	2017	Single	57/41	27/27	O	–	–	–	–
Hamaji (17)	T.S	2015	Single	413/104	41/41	O	–	–	–	–
Wang (18)	M.O.	2016	Single	106/74	35/35	–	Clin/clin	O	–	–

CSS, cancer-specific survival; DFS, disease-free survival; SBRT, stereotactic body radiotherapy; PET, positron emission tomography; T.S., thoracic surgeon; R.O., radiation oncologist; SEER, Surveillance, Epidemiology, and End Results; VACCR, Veterans Affairs Central Cancer Registry; Single, one institution; Path, pathological staging; Clin, clinical staging; O, factors considered in matching.

i.e., staging discordance between pathological *vs.* clinical staging. The OS difference attributable to stage migration can be calculated using the Japanese Lung Cancer Registry data (11), which consists of prospectively collected surgical data and has substantially contributed to the International Association for the Study of Lung Cancer (IASLC) through the transfer of these data. In the survey, the 3-year OS rate in surgical patients with clinical stage IA and IB NSCLC (UICC 7th) were 89.1% and 77.6%, respectively, and those with pathological stage IA and IB disease were 92.6% and 83.4%, respectively (11). Thus, the differences in OS between clinically *vs.* pathologically staged patients were 3.5% and 5.8%, respectively; this represents the differences in cancer death caused by stage migration. The difference among all stage I patients is estimated to be 4.1% (3.5%×3/4 + 5.8%×1/4), assuming the ratio of stage IA to IB patients is approximately 3:1 (11). Likewise, the difference in CSS by stage migration must also be 4.1%, because the survival difference is exclusively cancer-specific. In the analysis of Cao *et al.* (2), approximately two-thirds of the matched surgical patients were staged pathologically and the remaining one-third were staged clinically. In contrast, all patients who underwent SBRT were staged clinically (*Table 2*). To estimate a potential effect of staging discordance, a hypothetical assumption is made that the treatment efficacies of surgery and SBRT are equivalent (although the staging methods are different). Thereby, the hypothetical differences in CSS between surgery and SBRT, i.e., the CSS balance due to staging discordance, is calculated to be approximately 2.7% (4.1%×2/3). In contrast, the actual 3-year rates CSS in patients treated with surgery and SBRT in the analysis of Cao *et al.* were 81.5% and 76.7%, respectively (Cao *et al.*, Figure 3), with a difference of 4.8%. Therefore, the true CSS rate difference can be reduced to approximately 2.1% (range, 4.8–2.7%).

A second source of imbalance is histological subtype discordance. Most of the matched patients had pathologically confirmed disease. However, a substantial number of surgical patients would have been diagnosed only after surgery; such involved nodules are often difficult to biopsy for histological confirmation. In these patients without preoperative histological confirmation, the ratio of tumors with a major ground-glass opacity component was significantly higher than that of patients who underwent preoperative histological confirmation (19). In contrast, all patients who underwent SBRT had histologically confirmed disease before treatment, so their nodules were more likely to be composed of solid components and they tended to have a worse prognosis. Therefore, the surgical group may by default include patients with a better prognosis (20), and the difference in CSS between surgery and SBRT may be even smaller than that calculated above. Considering at least the two above imbalances, substantial biases cannot be excluded, even though the propensity analyses were technically performed well.

Surgery may actually result in better oncologic outcomes than SBRT. The extent of treatment is literally larger with lobectomy than with SBRT. In addition, mediastinal dissection (or sampling) is thought to be effective with respect to locoregional disease control. In fact, the

locoregional failure rate after SBRT is 10% (21), while it is 4.9–7.7% after surgery (22).

Randomized control trials (RCT) are the only ideal way to exclude the various biases mentioned above. However, recent RCTs comparing surgery to SBRT for medically operable patients with early-stage NSCLC closed prematurely due to poor accrual. Several ongoing RCTs for medically operable or high-risk operable patients may provide important information if they are completed and have sufficient accrual. In clinical practice, more patients are integrating their personal values into treatment, such as narrative-based medicine and shared decision-making. A result from a questionnaire survey overwhelmingly favored SBRT with respect to satisfaction, impression about toxicities, and quality of life (QOL) (23). Some patients may choose a treatment strategy based on QOL rather than treatment outcome. It would be helpful to focus on the various features of both treatment strategies, such as treatment schedules, time elapsed until social reintegration, frequencies and degrees of complications, and impacts on physical, mental, and social QOL (24). In fact, the numbers of patients undergoing SBRT are gradually increasing. The American Society of Clinical Oncology (ASCO) SBRT guidelines state that, for patients with high-risk, operable stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged within the multidisciplinary cancer care team (25). Patients should also be invited to join the treatment decision process while awaiting the results from RCTs.

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Footnote

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