Stereotactic body radiation therapy versus surgery for patients with stage I non-small cell lung cancer

Tomoki Kimura

Department of Radiation Oncology, Hiroshima University Hospital, Hiroshima City, 734-8551, Japan

Correspondence to: Tomoki Kimura. Department of Radiation Oncology, Hiroshima University Hospital, 1-2-3, Kasumi, Minami-ku, Hiroshima City, 734-8551, Japan. Email: tkkimura@hiroshima-u.ac.jp.

Abstract: Stereotactic body radiotherapy (SBRT) has been shown to be effective and safe for patients with inoperable stage I non-small cell lung cancer (NSCLC). In contrast, lobectomy is the standard treatment for patients with operable tumors, with sublobar resection (SLR) as an alternative for patients who cannot tolerate lobectomy. To investigate whether SBRT is an alternative to surgery, several randomized phase III trials were designed to compare lobectomy or SLR with SBRT, but those were closed because of slow accrual. Studies using propensity score-matching analyses to compare SBRT and lobectomy or SLR have reported that SBRT can be an alternative to both SLR and lobectomy in high-risk patients. Randomized phase III trials comparing lobectomy or SLR with SBRT are warranted in the near future.

Keywords: SBRT; non-small cell lung cancer (NSCLC); propensity score-matching; lobectomy; sublobar resectionv

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Introduction -What is SBRT?

Although the incidence rate of lung cancer has decreased over the last decade, its mortality rate remains the highest among all cancer-related deaths worldwide (1,2). Early detection, for example by CT examination, is very important to combat the high mortality rate due to lung cancer. Although lobectomy is the treatment choice for patients with early stage non-small cell lung cancer (NSCLC) (3,4), relatively few patients are candidates for lobectomy, as many are elderly or have poor pulmonary function. These patients are frequently treated with sublobar resection (SLR) or stereotactic body radiotherapy (SBRT), both of which have been shown to be effective and safe. SBRT, which delivers high radiation doses to focal lung tumors, has particularly helped to avoid radiation-induced damage to normal lungs (*Figure 1*). Treatment frequency is delivered via hypofractionated schedules, consisting of 3–5 fractions of 10- 15Gy per fraction. Toxicity may also be reduced by recent advanced technologies, including tumor-tracking, respiratory gating, image-guided radiotherapy systems.

This review summarizes comparisons of SBRT with surgery, including lobectomy and SLR, for patients with stage I NSCLC.

Current status of SBRT for patients with stage I NSCLC

SBRT for patients with medically inoperable stage I NSCLC

SBRT is widely used to treat patients with medically inoperable and peripherally located early stage NSCLC, having shown efficacy and safety in these patients (5-9). For example, a Japanese phase II trial, the Japan Clinical Oncology Group (JCOG) study 0403, reported that the 3-year overall survival (OS) and local control rates of SBRT (48 Gy in four fractions) for patients with c-stage IA medically inoperative NSCLC were 59.9% and 88%, respectively, with the rate of grade ≥4 toxicities being only 1% (8). The RTOG0236, phase II trial for patients with c-stage IA or IB medically inoperative NSCLC, found

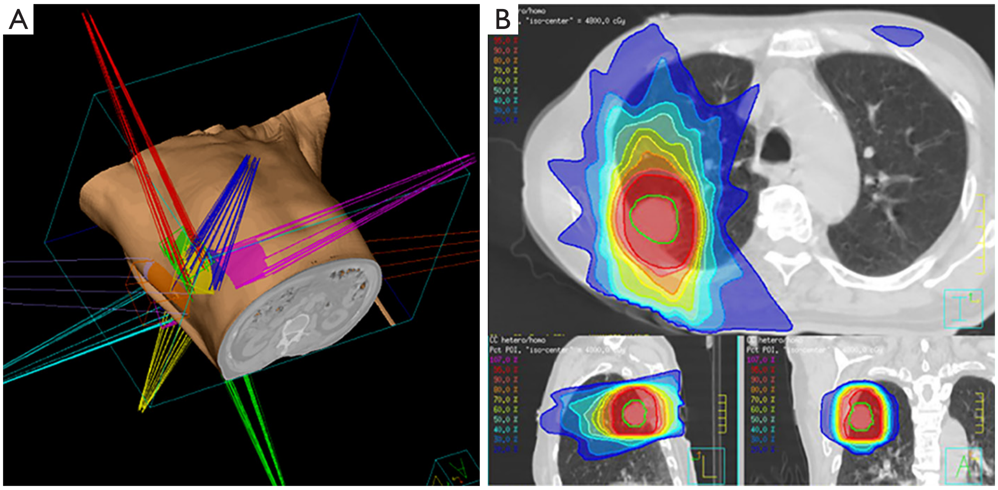

Figure 1 Procedure for stereotactic body radiotherapy (SBRT). (A) Image of beam direction; in this case, eight non-coplanar fields were used; (B) Dose distribution of SBRT for stage I non-small cell lung cancer: The high dose area (red) is focused on the tumor.

that a higher dose/fraction schedule for SBRT, such as 54 Gy in 3 fractions, resulted in a 3-year OS rate of 55.0 %, similar to that in JCOG0403. However, the local control rate, 97.6 %, was higher than that of JCOG0403, likely because of its higher dose/fraction schedule. The rate of grade ≥4 toxicities was 3.6% (7). The findings of several studies suggested that SBRT is effective and safe for patients with medically inoperable early NSCLC (*Table 1*). Moreover, the guidelines of the National Comprehensive Cancer Network (NCCN), as well as Japanese guidelines, have recommended SBRT as standard treatment for these patients (3,4).

In contrast, the optimal dose/fraction schedule remains unclear. A Japanese multi-institutional cohort study suggested that the optimal dose/fraction schedule be based on the biologically effective dose (BED) (10). For example, the effects of various dose/fraction schedules, consisting of different fraction sizes and total doses, were assessed using the BED in a linear-quadratic model (11). In that study, the BED was defined as $nd(1 + d/\alpha/\beta)$, with gray units, where n is the fractionation number, d is the daily dose, and α/β is assumed to be 10 for tumors. The authors of that study concluded that local control and survival rates were better with a BED of ≥100 Gy than of <100 Gy for all dose/fraction schedules. A meta-analysis of 34 observational studies containing a total 2,587 patients also assessed the optimal BED range for treatment of c-Stage I NSCLC (12). That study found that Grade 3–5 adverse events were more frequent in patients with high BED (>146 Gy), suggesting that SBRT using a medium (83.2–106 Gy), or medium-to-high (106–146 Gy) BED may be more beneficial than SBRT using a low (<83.2 Gy) or high (>146 Gy) BED. To determine the optimal dose/fraction schedule, we started a randomized phase III study (JCOG1408) in February 2016 comparing 42 Gy in four fractions (BED_{10}: 86.1 Gy) with 55 Gy in four fractions (BED_{10}: 130.6 Gy) for patients with medically inoperable stage IA NSCLC and small lung lesions clinically diagnosed as primary lung cancer (13). The standard arm, 42 Gy in four fractions prescribed at the D95% of the planning target volume, which is considered equal to 48 Gy in four fractions at the isocenter using an old dose calculation algorithm, is the standard treatment in Japan for medically inoperable stage IA NSCLC.

SBRT for patients with medically operable stage I NSCLC

Compared with the number of publications evaluating SBRT for medically inoperable early NSCLC, fewer have assessed SBRT for medically operable early NSCLC (8,14-16). A retrospective study evaluation SBRT for 87 patients with medically operable stage I NSCLC using a Japanese multi-institutional database studied several dose/fraction schedules, involving 45–72.5 Gy in 3–10 fractions (median BED_{10} 116 Gy; range, 100–141 Gy) (14). That study reported that 5-year OS and local control rates were 72% and 62%, respectively, in the Stage IA subgroup and 92% and 73%, respectively, in the Stage IB subgroup, with no severe toxicities. In the phase II JCOG0403 trial,

Table 1 Treatment results of SBRT for patients with medically inoperable non-small cell lung cancer

Author (year)	Stage (stage IB)	Study design	N	Dose/fraction (BED_{10})[#]	Prescription method	3-year overall survival	3-year local control	Toxicity grade 3≥ (Grade 4≥)
Baumann P (2009) (5)	IA/B 30.0%	Phase II	57	45 Gy/3 fr (112.5 Gy)	PTV marginal	60%	92%	29.9% 1.8%
Fakiris AJ (2009) (6)	IA/B 51.4%	Phase II	70	IA: 60 Gy/3 fr (180 Gy), IB: 66 Gy/3 fr IB: 66 Gy/3 fr (192 Gy)	PTV marginal	42.7%	N.A.*	17.1% 8.6%
RTOG0236 (2010) (7)	IA/B 20.0%	Phase II	55	54 Gy/3 fr (151.2 Gy)	PTV marginal	55%, (5 y 40%)	97.6%, (5 y 93 %)	16.3% 3.6%
JCOG0403 (2015) (8)	IA	Phase II	100	48 Gy/4 fr (105.6 Gy)	Isocenter	59.9%	88%	10.6% 1%
RTOG0915 (9)	IA/B 11.1%	Randomized Phase II	45	48 Gy/4 fr (105.6 Gy)	PTV marginal	77.7 % (2 y)	92.7 % (1 y)	13.3% NA*
RTOG0915 (9)	IA/B 18.0%	Randomized Phase II	39	34 Gy/1 fr (150 Gy)	PTV marginal	61.3 % (2 y)	97 % (1 y)	10.3% NA*

*NA, not available, [#]BED_{10}, biologically effective dose based on α/β =10 Gy.

involving 48 Gy in 4 fractions, the 3-year OS and local control rates were 76.0% and 88%, respectively (6). In another phase II study, RTOG0618, involving 54 Gy in 3 fractions, the 2-year OS and local control rates were 84.4% and 92.3%, respectively (16). No patients in these two phase II trials experienced grade ≥ 4 toxicity. *Table 2* summarizes treatment results for patients with medically operable NSCLC, showing that the survival rates after SBRT and surgery were comparable. However, because of the lack of phase III trials comparing surgery with SBRT, guidelines continue to recommend surgery, especially lobectomy, as standard treatment for medically operable patients (8,9).

SBRT versus surgery for patients with stage I NSCLC

SBRT versus lobectomy for patients with medically operable stage I NSCLC

SBRT for patients with medically operable stage I NSCLC was found to result in a local control rate >90% and a 3-years OS rate of 70- 80% (*Table 2*). However, because mediastinal lymph node dissection or sampling is usually performed during lobectomy, concerns remain about the risk of local or nodal recurrence after SBRT, either of which could lead to poorer OS than after lobectomy. SBRT and lobectomy having been compared using propensity score-matching (PSM) analyses (*Table 3*) (17-23). A survey of the Surveillance, Epidemiology, and End Results (SEER) database from 2003 to 2009 assessed, OS in a large number of patients with early-stage, node-negative NSCLC who underwent lobectomy (n=7,215), or SBRT (n=382) (19). Prior to maching, SBRT was associated with a lower risk of death [hazard ratio (HR), 0.45; 95% confidence interval (CI), 0.27–0.75; P<0.001] during the 6 months, but a higher risk of death (HR, 1.66; 95% CI, 1.39–1.99; P<0.001) after 6 months. After PSM, resulting in 251 well-matched pairs, the two modalities were associated with a similar risk of OS (HR, 1.01; 95% CI: 0.74–1.38; P=0.94). These findings suggested that lobectomy was the optimal treatment for older individuals able to undergo surgery. However, SBRT was promising for frail patients and those of advanced age because of a lower risk of periprocedural mortality and encouraging long-term survival. Another study, 64 matched pairs found 3-year OS rates were similar in patients who underwent lobectomy and SBRT (77% *vs.* 80%, P=0.803) (23). A study of 73 matched pairs reported, although 3-year OS rates tended to favor surgery, 5-year OS rates were similar in patients who underwent lobectomy and SBRT (80% *vs.* 53%, P= 0.082) (20).

These studies from western countries suggested that

Table 2 Treatment results of SBRT for patients with medically operable non-small cell lung cancer

Author (year)	Stage (stage IB)	Study design	N	Dose/fraction (BED_{10})[#]	Prescription method	3-year overall survival	3-year local control	Toxicity grade 3≥ (Grade 4≥)
Onish H (2011) (14)	IA/B 25.3%	retrospective	87	45–72.5 Gy/3–10 fr (100–144 Gy)	Isocenter	IA: 72% (5y) IB: 62% (5y)	IA: 92 % (5 y) IB: 73 % (5 y)	9.2% 0%
Lagerwaard FJ (2012) (15)	IA/B 40.1%	retrospective	177	60 Gy/3– 8 fr (105–180 Gy)	PTV marginal	84.7%	93%	5% NA*
JCOG0403 (2015) (8)	IA	Phase II	64	48 Gy/4 fr (105.6 Gy)	Isocenter	76%	86%	6.2% 0%
RTOG0618 (2013) (16)	IA/B 11.5%	Phase II	26	54 Gy/3 fr (151.2 Gy)	PTV marginal	84.4% (2 y)	92.3% (2 y)	15.4% 0%

*NA, not available; [#]BED_{10}, biologically effective dose based on α/β =10 Gy.

OS rates were similar in patients who underwent SBRT and lobectomy. Although STARS trial (Randomized study to compare CyberKnife to surgical resection in stage I non-small cell lung cancer: NCT00840749) was initiated in 2009, and the ROSEL trial (Trial of either surgery or stereotactic radiotherapy for early stage IA lung cancer: NCT00687986) was initiated in 2008, these two randomized phase III trials had to be closed because of slow accrual. A pooled analysis of the 58 patients enrolled in these two trials and randomized to SBRT (n=31) and lobectomy (n=27) found that these two groups had 3-year OS rates of 95 % (95 % CI, 85–100%) and 79% (95% CI: 64–97%), respectively (HR, 0.14; 95% CI, 0.017–1.190; log-rank P= 0.037) (21). Although these results were encouraging, there were several limitations, such as the small number of patients, the study not being a true randomized phase III trial, and the poorer results of lobectomy (3-year OS: 79%) compared with studies in Japan, such as JCOG0201, which reported a 5-year OS rate of 90.6% (24).

Two Japanese reports found that OS rates after PSM were significantly better for lobectomy than for SBRT (19,22). These differences were thought to be due to the lower mortality rate after lobectomy and the higher cause-specific survival (CSS) rate in the lobectomy group. Regional lymph node control was found to be similar in patients who underwent lobectomy and SBRT (19), suggesting that routine systematic mediastinal LN dissection did not have a therapeutic effect, but rather identified candidates for adjuvant chemotherapy, which may be associated with a significant difference in distant control when compared with SBRT.

SBRT versus sublobar resection for patients with stage I NSCLC at high risk for lobectomy

Theoretically, due to the omission of mediastinal lymph node dissection or sampling, SLR may be similar to SBRT as a local treatment modality for patients at high risk for lobectomy. According to NCCN guidelines, SBRT is also an appropriate option for patients at high surgical risk who are able to tolerate SLR but not lobectomy, such as aged >75 years and those with poor lung function (8). PSM analyses have compared SBRT and SLR (*Table 4*) (25-34). A survey of the SEER database, comparing SLR and SBRT in 112 pairs of PSM patients in from 2001 to 2007, found that these two modalities were associated with similar OS rates (HR, 0.82; 95% CI: 0.45–1.12; P=0.38) (27). A comparison of SLR and SBRT, based on a median age of 76 years, a performance status of 0–1, a median tumor diameter < 20 mm, a median 1 second forced expiratory volume (FEV1) of <1.8 L and a median Charlson comorbidity index of 1, found that, before PSM, the 5-year OS rate was higher in the SLR than in the SBRT group (60.5% *vs.* 40.3%, P=0.008) but 5-year CSS rates were similar (26.3% *vs.* 33.8%, P=0.215). A study of 53 matched pairs found that patient series, 5-year OS (55.6% *vs.* 40.4%, P=0.124) and CSS (30.3% *vs.* 35.3%, P=0.427) rates were similar in the SLR and SBRT groups (29). Most of the studies cited in *Table 4* showed no significant differences in OS and CSS between SBRT and SLR after PSM. These similar outcomes may have been due to the inclusion of both groups of patients with comorbidities and to both modalities being local treatment. Prospective trials will likely show that OS and CSS are similar in patients undergoing SBRT and

Table 3 Lobectomy *vs.* SBRT using Propensity score matching

Author (year)	Data source	N	Surgery	SBRT	OS (unmatched)		OS (matched)		Conclusions
					Surgery	SBRT	Surgery	SBRT	
Verstegen NE (2013) (17)	c-I/II	Surgery: 86 SBRT: 527 Matched: each 64	Lobectomy	60 Gy/5 fr (BED_{10} ≥100 Gy)	-		77% (3 y)	80% (3 y)	OS rates did not differ significantly
						P= 0.803			
Shirvani SM (2014) (18)	c-IA/IB SEER database (2003- 2009)	Surgery: 7,215 SBRT: 382 Matched: each 251	Lobectomy	Several dose/ fraction schedule BED_{10} ≥100 Gy)	Lobectomy *vs.* SBRT (after initial 6 months): HR 1.66 (95% CI: 1.39–1.99), P<0.001		Lobectomy *vs.* SBRT: HR 1.01 (95% CI: 0.74-1.38), P= 0.94		Lobectomy is optional for older adults able to undergo surgery. SBRT is promising for frail patients and those of advanced age because of a lower risk of periprocedural mortality and encouraging long-term survival
Eba J (2014) (19)	c-IA JCOG0203/0403 database	Surgery: 219 SBRT: 40 Matched: each 21	Lobectomy	48 Gy/4 fr	87.7% (5 y)	67.0% (5 y)	HR: 9.00 (1.14–71.04), P=0.037		The point estimates of HR for OS favored lobectomy over SBRT in a limited number of patients. Randomized controlled trials are needed for a valid comparison to evaluate the non-inferiority of SBRT
					HR 1.51, P= 0.28				
Mokhles S (2015) (20)	c-IA/B	Surgery: 96 SBRT: 481 Matched: each 73	Lobectomy	54–60 Gy/ 3–8 fr	–		80% (5 y)	53% (5 y)	OS rates did not differ significantly in propensity matched patients with stage I NSCLC treated surgically or with SBRT
							P=0.082		
Chang JY (2015) (21)	c-IA/IB STARS + ROSEL database	Surgery: 27 SBRT: 31	Lobectomy	54 Gy/3 fr	–		79% (3 y)	95% (3 y)	SBRT may be an option for treating operable stage I NSCLC
							P=0.037		
Hamaji M (2015) (22)	c-IA/B	Surgery: 412 SBRT: 104 Matched: each 41	Lobectomy	Median: 48 Gy/4 fr	78.3% (5 y)	40.6% (5 y)	68.5% (5 y)	37.3% (5 y)	VATS lobectomy may offer significantly more favorable long-term outcomes than SBRT in potentially operable patients with biopsy proven clinical stage I NSCLC
					P< 0.0001		P=0.0016		
Rosen JE (2016) (23)	c-IA/B National Cancer database	Surgery: 13,562 SBRT: 1,781 (operable) Matched: 1,781	Lobectomy	Variable	-		59% (5 y)	29% (5 y)	Among healthy patients with clinical stage I NSCLC, lobectomy is associated with a significantly better outcome than SBRT
							P<0.001		

Table 4 SLR* or SLR/Lobectomy *vs.* SBRT using Propensity score matching

Author (year)	Data Source	N	Surgery	SBRT	OS (unmatched)		OS (matched)		Conclusions
					Surgery	SBRT	Surgery	SBRT	
Palma D (2011) (25)	c-IA/B 17 centers in Netherland	Surgery: 109 SBRT: 81 Matched: each 60	Lobectomy: 82 % Sublobar: 15 % Pneumonectomy: 3%	60 Gy/5 fr	- P=0.22		60% (3 y)	42% (3 y)	Similar OS outcomes are achieved with surgery or SBRT for stage I NSCLC in elderly patients
Shirvani SM (2012) (26)	c-IA/IB SEER database (2001- 2007)	Surgery: 1,278 SBRT: 124 Matched: each 112	Sublobar	Several dose/ fraction schedule (BED_{10} ≥100 Gy)	-		Sublobar *vs*. SBRT: HR 0.82 (95% CI: 0.45-1.12), P= 0.38		Survival after SBRT was similar to that after sublobar resection
Varlotto J (2013) (27)	c-IA/IB	Surgery: 180 SBRT: 137 Matched: each 72 (lobectomy) Matched: each 17 (sublobar)	Lobectomy: 132 Sublobar: 48	60 Gy/3 fr (BED10 ≥100 Gy)	P=0.004 86.3% (5 y: sublobar) 31.7% (5 y) P=0.003		69.2% (5 y: lobectomy)	33.7% (5 y)	OS was superior in SLR compared with SBRT matched pairs base. However, a multivariate analysis that included propensity scores as a covariate revealed that the hazard ratio for OS was not significant
Crabtree TD (2014) (28)	c-IA/B	Surgery: 458 SBRT: 151 Matched: each 56	Lobectomy: 78 % Sublobar: 18 % Pneumonectomy: 4 %	54 Gy/3 fr (BED_{10} ≥100 Gy)	78% (3 y)	47% (3 y)	60% (3 y) P= 0.05	52% (3 y)	Although surgical resection seems to result in better OS and DFS versus SBRT, matching these disparate cohorts of patients remains challenging
Matsuo Y (2014) (29)	c-IA/IB	Surgery: 65 SBRT: 115 Matched: each 53	Sublobar	48 or 56 Gy/4 fr 60 Gy/8 fr (central)	60.5% (5 y) P= 0.008	40.3% (5 y)	55.6% (5 y) P= 0.124	40.4% (5 y)	SBRT can be an alternative treatment option to SLR for patients who cannot tolerate lobectomy
Zheng X (2014) (30)	c-IA/IB meta-analysis	Surgery: 7,071 SBRT: 4,850 Matched: operability, <70 y.o.	Lobectomy: 86.2 % Sublobar 13.8 %	Several dose/ fraction schedules (BED10 ≥100 Gy)	66.1% (5y: lobectomy) 71.7% (5y: sublobar)	41.2% (5y)	68% (5y: lobectomy) 66% (5y: sublobar)	82% (5y)	After adjustment for these differences, OS do not differ significantly between SBRT and surgery in patients with operable stage I NSCLC

Table 4 (*continued*)

Table 4 *(continued)*

Author (year)	Data Source	N	Surgery	SBRT	OS (unmatched)		OS (matched)		Conclusions
					Surgery	SBRT	Surgery	SBRT	
Port JL (2014) (31)	c-IA	Surgery: 76 SBRT: 23	Sublobar (Wedge ± Brachy)	Median: 48 Gy/4 fr	- P= 0.357		87% (3 y)	75% (3 y)	Patients with clinical stage IA NSCLC treated by SBRT appear to have higher overall disease recurrence than those treated by SLR. However, there was no significant difference in DFS
Puri V (2015) (32)	c-IA/B	Surgery:111,731 SBRT: 5,887 Matched: each 5355 Matched: each 4555 (sublobar)	Lobectomy: 71.4 % Sublobar: 27.4 % Pneumonectomy: 1.2 %	Median: 54 Gy	61.7% (3 y: sublobar) 46% (3 y)		68% (3 y)	47% (3 y)	Patients selected for surgery have improved survival compared with SBRT
Ma L (2016) (33)	Meta-analysis	Surgery: 3,436 SBRT: 4,433 Matched: age, operability	Variable	Variable	82.8% (3 y) Significant difference	6% (3 y)	84% (3 y) No significant difference	87% (3 y)	After adjusting for these differences, OS and DFS did not differ significantly between the two techniques
Wang P (2016) (34)	c-IA/B	Surgery: 106 SBRT: 74 Matched: each 35	Lobectomy: 60.4 % Sublobar: 39.6 %	60 Gy/3–8 fr: 90.5 % 54 Gy/3 fr: 9.5 %	69% (5y) P=0.0007	44.6% (5y)	67.8% (5y) P=0.07	47.4% (5y)	There were no differences in OS; SBRT is an alternative treatment option to surgery in elderly NSCLC patients who cannot tolerate lobectomy

SLR, suggesting that SBRT may be an alternative to SLR in high-risk patients who cannot tolerate lobectomy because of medical comorbidities.

Conclusions

Many studies using PSM analysis founded that SBRT can be an alternative treatment option to SLR in high-risk patients who cannot tolerate lobectomy because of medical comorbidities, but also as well as being an alternative to lobectomy. Randomized phase III trials comparing lobectomy or SLR with SBRT are warranted in the near future.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.05.17). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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