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Review

Radiotherapy for small cell lung cancer in current clinical practice guidelines☆

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ABSTRACT

Several guidelines including radiotherapy recommendations exist worldwide for the treatment of small cell lung cancer (SCLC). To evaluate the differences in radiotherapy recommendations we conducted a systematic review. PubMed and the sites of medical societies were searched for SCLC guidelines published in either English, Chinese, or Dutch. This was limited to January 2018 till February 2021 to only include up-to-date recommendations. Data was extracted and compared regarding the guideline's development method and radiotherapy recommendations. Eleven guidelines were identified (PubMed n=4, societies n=7) from Spain (n=1), Canada (n=1), America (n=3), United Kingdom (n=1), the Netherlands (n=1), and China (n=3), respectively. Nine guidelines assessed the strength of evidence (SOE) and specified the strength of recommendation (SOR), although methods were different. The major radiotherapy recommendations are similar although differences exist in thoracic radiotherapy (TRT) dose, time, and volume. Controversial areas are TRT in resected stage I-IIA (pN1), prophylactic cranial irradiation (PCI) in resected as well as unresected stage I-IIA, stereotactic body radiation therapy (SBRT) in unresected stage I-IIA, PCI time, and PCI versus magnetic resonance imaging (MRI) surveillance in stage IV. The existence of several overlapping guidelines for SCLC treatment indicates that guideline development is (unnecessarily) repeated by different organizations or societies. Improvement could be made by better international collaboration to avoid duplicating unnecessary work, which would spare a lot of time and resources. Efforts should be made to work together on controversial or unknown fields.

1. Introduction

Small cell lung cancer (SCLC) accounts for approximately 13%-20% of all newly diagnosed lung cancers[1,2]. As a rapidly aggressive disease, the 5-year survival is only 7%[3]. Although significant progress has been made in the treatment for non-small cell lung cancer (NSCLC), such as the introduction of targeted therapy and immunotherapy, in the last decades only limited progress has been made in the treatment of SCLC. Recent developments in SCLC treatment are mainly regarding stereotactic body radiation therapy (SBRT) in very early stage SCLC[4-6], and the use of prophylactic cranial irradiation (PCI)[7,8], thoracic radiotherapy (TRT)[9,10], and immune checkpoint inhibitors (ICI)[11-14] in metastatic SCLC. Several guidelines have been updated accordingly. Based on different interpretation of clinical trials, the specific conditions of different countries and regions, and the respective state of economy and social development, guidelines could be different across organizations and countries. In this systematic review we provide an overview of existing guidelines with a focus on guideline developing methods and radiotherapy recommendations.

2. Methods

We systematically searched PubMed for existing SCLC guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[15]. As we selected only the most up-to-date versions, we limited our search to guidelines published from January 1, 2018 till the search date (Feb 28, 2021). Specific guidelines only providing recommendations on radiotherapy techniques and tar-

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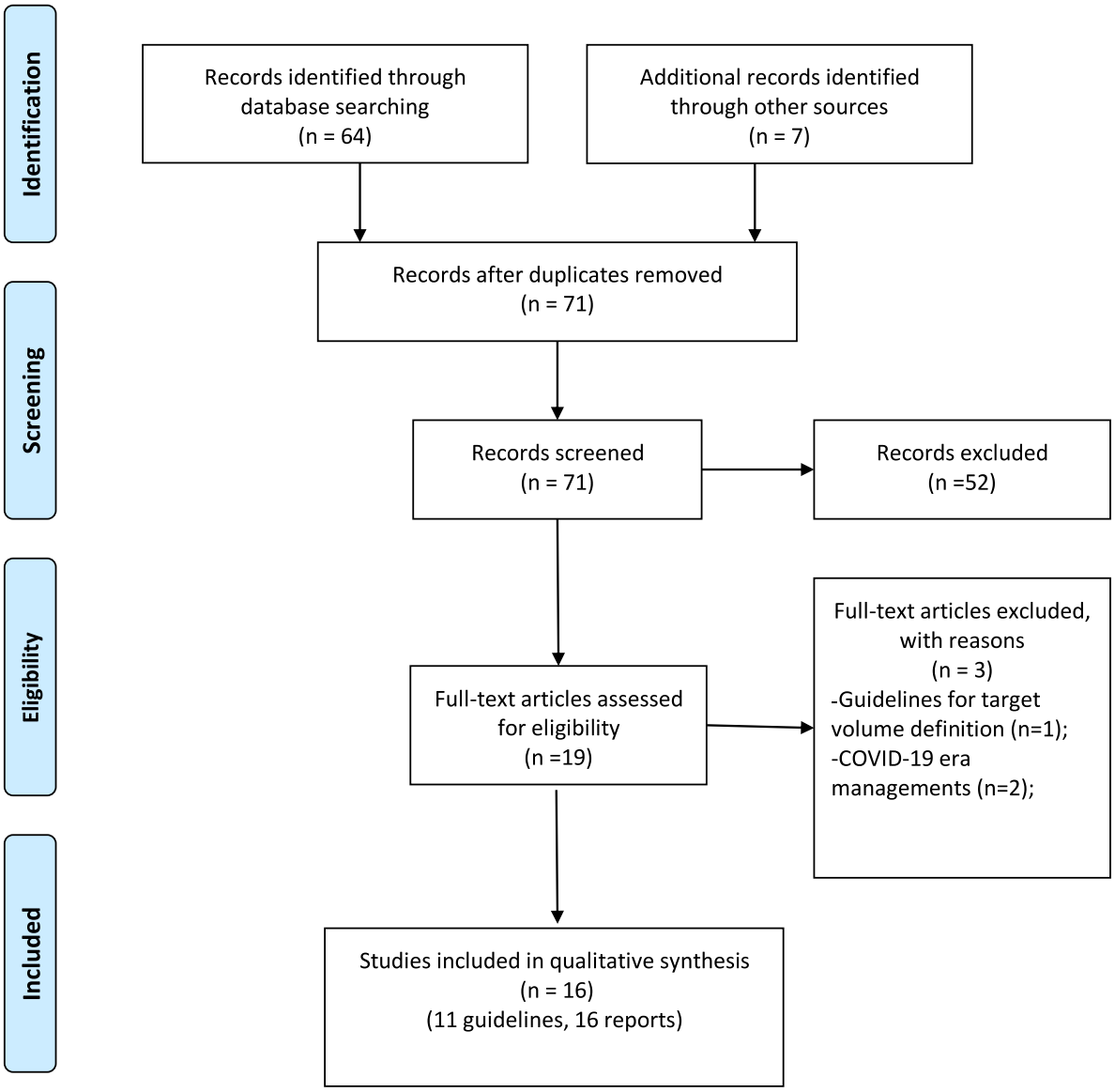

Fig. 1. PRISMA flow diagram.

get volumes were excluded. The main searched terms were "SCLC" and "guideline" (Appendix 1). This search was limited to English language only.

Furthermore, we searched whether national and international societies [the National Comprehensive Cancer Network (NCCN) (America), the European Society for Medical Oncology (ESMO) (Europe), the National Institute for Health and Care Excellence (NICE) (United Kingdom, UK), the Federatie Medisch Specialisten (FMS) (Netherlands), and the Chinese societies] had a SCLC guideline in either English, Chinese, or Dutch (languages in which guidelines could be interpreted by the authors) and we also selected these guidelines.

Data from these guidelines was extracted and compared regarding the method of development of the guideline, as well as the recommendations regarding the use of radiotherapy in the different disease stage (very early, limited, and extensive disease) and in relation to ICI use. Details about radiotherapy techniques were not specified in this review.

3. Results

3.1. Guidelines selection

A total of 64 records were yielded in PubMed, of which four guidelines were eligible: the Cancer Care Ontario's (CCO's) Lung Cancer Disease Site Group (DSG) (CCO's DSG) (Canada, 2018)[16], the Spanish Society of Medical Oncology (SEOM) (Spain, 2020)[17], the American Society for Radiation Oncology (ASTRO) (America, 2020)[18], and the American Radium Society (ARS) Thoracic Appropriate Use Criteria (AUC) Committee (ARS AUC) (America, 2020)[19,20]. Additionally, seven guidelines were identified through searching of the societies: NCCN (2021)[21], ESMO (2021)[22], NICE (2019)[23], FMS (2019)[24-26], the Chinese Society of Clinical Oncology (CSCO) (2020)[27], the Chinese Society for Radiation Oncology (CSTRO) (2020)[28], and the Chinese Medical Association (CMA) (2019)[29] (Fig. 1, Table 1).

3.2. Developing methods of guidelines

All guidelines are evidence based, of which three are based on non-systematic literature reviews (SEOM[17], NCCN[21], ESMO[22]), five are based on systematic reviews (CCO[16], ARS[19,20], ASTRO[18], FMS[24-26], NICE[23]), and three have no related information (CSCO[27], CSTRO[28], CMA[29]). Nine guidelines assessed the strength of evidence (SOE)[16-20,22-27,30] and specified the strength of recommendation (SOR)[17-20,22-28,30], but both the assessment methods as well as the reported forms are different. Eight committees assessed the overall SOR of all related evidences[17-20,22,24-28,30], while the NICE committee assessed

Table 1
Summary of Guidelines.

Guideline (version), online year	Country	Methods	Quality assessment	Strength of evidence	Strength of recommendation
North America					
CCO (2018), 2018[1]	Canada	Practice Guidelines Development Cycle, includes systematic review	Cochrane Risk of Bias tool	High, Moderate, Low, EC	NI
ASTRO (2020), 2020[2]	America	Systematic review	Consensus-building methodology and system; Consensus is evaluated using a modified Delphi approach	High, Moderate, Low, EO	Strong, Conditional
ARS (2020), 2020[3,4]	America	Systematic review	Assessed according to the ARS criteria; Quality descends from category 1 to category 4; A well established methodology (modified Delphi)	S-strong; M-moderate; L-limited; EC-expert consensus; EO-expert opinion	↑ Strong recommendation; - Not strong, not weak; ↓ Weak recommendation
NCCN (2.2021), 2021[5]	America	Review, real-time updates	Panel meeting discussion	See SOR	Category 1, 2A, 2B, and 3*
Europe					
ESMO (2021), 2021[6]	Europe	Review, the ESMO standard operating procedures for clinical practice guidelines development	Adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System	Level of evidence descends from I to V	The grade of recommendations changes from strongly recommended (A) to never recommended (E)
NICE (2019), 2019[7]	England	The NICE guidelines developing manual, includes systematic review	Based on AGREE Enterprise's Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument	Each study: high, moderate, low, very low[&]	Wording: offer, advise, ask about, must; consider; do not offer, must not
FMS (2019), 2019[8-10]	The Nether-lands	Systematic review	Evidence based, according to the AGREE criteria for guidelines	Quality descends in the order: A1, A2, B, C, D (EO)	The recommendation strength descends in the order: Level 1, 2, 3, 4 (EO)
SEOM (2019), 2020[11]	Spain	Review	The Infectious Diseases Society of America Grading System	I–III indicate the descending quality of evidence	A–E signify the strength of the recommendation changing from for to against use
China					
CSCO (2020), 2020[12]	China	Based on evidence, accessibility, and EO	Guideline Committee	Quality descends in the order: 1A, 1B, 2A, 2B, 3	I, II, III, not recommend/against
CSTRO (2020), 2020[13]	China	Based on evidence and EO	NI	NI	NI
CMA (2019), 2019[14]	China	International guidelines and the actual situation in China	Guideline Committee	NI	Category 1, 2A, 2B, and 3

* All of the recommendations are category 2A unless otherwise noted.
& The NICE committee assesses the quality for each study, instead of making a whole assess for all the referred studies.
Abbreviations: EC, expert consensus; EO, expert opinion; NI, no information; SOR, strength of recommendation (grade of recommendation);
Abbreviations for guidelines:
CCO, the Cancer Care Ontario's (CCO's) Lung Cancer Disease Site Group (DSG);
ASTRO, the American Society for Radiation Oncology;
ARS, the American Radium Society (ARS) Thoracic Appropriate Use Criteria Committee (AUC);
NCCN, the National Comprehensive Cancer Network;
ESMO, the European Society for Medical Oncology;
NICE, the National Institute for Health and Care Excellence;
FMS, Federatie Medisch Specialisten;
SEOM, the Spanish Society of Medical Oncology;
CSCO, the Chinese Society of Clinical Oncology;
CSTRO, the Chinese Society for Radiation Oncology;
CMA, the Chinese Medical Association.

the SOR for each study[23]. SOE and SOR classification are different for the guidelines as presented in Table 1. The quality assessments are also different. Two committees used the Infectious Diseases Society of America grading system or the adapted version (SEOM[17], ESMO[22]), two used the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (NICE[23], FMS[24-26]), two used the modified Delphi (ASTRO[18], ARS[19,20]), CCO used the Cochrane Risk of Bias tool[16], three depended on the committee discussion (NCCN[21], CSCO[27], CMA[29]), and CSTRO did not specify related information[28] (Table 1).

3.3. Recommendations of guidelines

3.3.1. Stage I–IIA (cT1–T2, N0, M0)

For patients with resected stage I-IIA SCLC, guidelines that provide recommendations state that TRT in patients with pathological N2 can be considered (SEOM[17], ASTRO[18], ARS[19,20], NCCN[21], ESMO[22], FMS[24-26], CSCO[27], CMA[29], CCO[16], NICE[23]) or R1-2 (SEOM[17], ARS[19,20], CMA[29]), but for pN1, the recommendations are discrepant. The SEOM[17], ARS[19,20], CSTRO[28], and CMA[29] recommend TRT, NCCN[21] and CSCO[27] suggest that TRT may be considered, while ASTRO does not recommend TRT[18], and other guidelines have no related information. PCI is recommended in FMS[24-26] and CSCO[27], not recommended in SEOM[17], and others state PCI can be considered (ASTRO[18], ARS[19,20], ESMO[22], CSTRO[28], CMA[29], NCCN[21]) (Table 2).

For patients with stage I-II disease not surgically treated, chemoradiotherapy is recommended in all guidelines. Six guidelines further suggest that SBRT could be considered (SEOM[17], ASTRO[18], ARS[19,20], CSCO[27], CSTRO[28], NCCN[21]). PCI is recommended in CSCO[27], but not recommended in SEOM[17]. ASTRO[18] and ESMO[22] manage PCI the same as in resected stage I-IIA. ARS recommends PCI in patients who are at

Table 2
Recommendations of Guidelines: Stage I–IIA (cT1–T2, N0, M0)*.

Guideline (version), online year	Resected		Not resected		
	RT	PCI	SBRT**	RT**	PCI
North America					
CCO (2018), 2018[1]	NI	NI	NI	See Table 3	NA
ASTRO (2020), 2020[2]	R1-2: yes [Conditional, EO]; pN2: yes [Conditional, EO]; pN0-1: no	Stage I: no, MRI surveillance instead [Conditional, Low]; Stage IIA, age <70 years, PS 0-2, response: yes [Strong, High];	Yes [Strong, Moderate]	Yes	Stage I: no, MRI surveillance instead [Conditional, Low]; Stage IIA, age <70 years, PS 0-2, response: yes [Strong, High];
ARS (2020), 2020[3,4]	R1-2: yes [↑, EC]; pN+: yes [↑, EC]; pN0: no [↑, EC]	At risk for being lost to follow-up: yes [-, L]	Yes [-, L]	CCRT [↑, S]	At risk for being lost to follow-up: yes [-, EO]
NCCN (2.2021), 2021[5]	pN2: yes; pN1: may be considered	See Table 3	May be considered	Yes	See Table 3
Europe					
ESMO (2021), 2021[6]	pN2 and/or R1-2: CCRT [A, IV]	Shared decision making [C, V]	NI	PS 0-1: CCRT [A, I]; PS ≥2: SCRT [B, V]	Shared decision making [C, V]
NICE (2019), 2019[7]	NI	NI	NI	See Table 3	See Table 3
FMS (2019), 2019[8-10]	pN2: yes [3, C]	Yes [3, C]	NI	See Table 3	See Table 3
SEOM (2019), 2020[11]	pN+: SCRT/CCRT [A, II] ***	No	May be [B, III]	Yes	No
China					
CSCO (2020), 2020[12]	R1-2: NI pN1: can be considered [I, category 2A]; pN2: yes [I, category 2A]; RT dose: 50 Gy	Yes [II, category 1]	Yes [I, category 2A]; SBRT dose: 50-60 Gy in 5 fractions	Yes [I, category 1]	Yes [II, category 1]
CSTRO (2020), 2020[13]	pN+: yes; Dose: 50 Gy in 25 fractions; R1/R2: radical dose for the local residual lesions	pN+: yes	Yes	CCRT	Based on each patient's specific status and willingness
CMA (2019), 2019[14]	pN+: SCRT/CCRT [category 2A]	According to patients' conditions [category 1]	NI	See Table 3	See Table 3
Summary	RT is recommended in patients with R1-2 or pN2 but recommendations are discrepant in patients with pN1	PCI is controversial	SBRT is less consensus	Chemoradiotherapy is recommended	PCI is controversial

* Consistent recommendations are colored as yellow ( ); less consensus as green ( ); inconsistent as turquoise ( ).
** Either SBRT or RT is recommended.
*** Recommendations are recorded as [SOR, SOE].
Abbreviations: CCRT, concomitant chemoradiotherapy; MRI, magnetic resonance imaging; NA, non-applicable; NI, no information; PCI, prophylactic cranial irradiation; SBRT, stereotactic body radiation therapy; SCRT, sequential chemoradiotherapy; SOE, strength of evidence (quality of evidence, level of evidence); SOR, strength of recommendation (grade of recommendation); RT, radiotherapy.
Abbreviations for guidelines:
CCO, the Cancer Care Ontario's (CCO's) Lung Cancer Disease Site Group (DSG);
ASTRO, the American Society for Radiation Oncology;
ARS, the American Radium Society (ARS) Thoracic Appropriate Use Criteria Committee (AUC);
NCCN, the National Comprehensive Cancer Network;
ESMO, the European Society for Medical Oncology;
NICE, the National Institute for Health and Care Excellence;
FMS, Federatie Medisch Specialisten;
SEOM, the Spanish Society of Medical Oncology;
CSCO, the Chinese Society of Clinical Oncology;
CSTRO, the Chinese Society for Radiation Oncology;
CMA, the Chinese Medical Association.

risk for being lost to follow-up[19,20]. CSTRO suggests that this can be decided based on each patient's specific status and willingness[28]. Others manage it the same as in stage IIB-IIIC (NCCN[21], NICE[23], FMS[24-26], CMA[29]) (Table 2).

3.3.2. Stage IIB–IIIC (cT3–4, N0, M0; T1–4, N1–3, M0)

For patients with stage IIB-IIIC disease, all guidelines prefer concurrent chemoradiotherapy (CCRT). Most guidelines advise to start radiotherapy (45 Gy twice-daily [BID] or 60-70 Gy once-daily [QD] [SEOM[17], ASTRO[18], ARS[19,20], NCCN[21], NICE[23], CSCO[27], CSTRO[28], CMA[29], CCO[16]]) preferably at the first or second cycle of chemotherapy (SEOM[17], ASTRO[18], ARS[19,20], NCCN[21], NICE[23], ESMO[22], CSCO[27], CSTRO[28], CMA[29]). The CCO[16] advises to start radiotherapy as early as possible, and the FMS[24-26] advises to start within 30 days from the start of chemotherapy. The ESMO[22] and the FMS[24-26] specifically advise 45 Gy BID.

As for the radiotherapy volume, the SEOM advises that the primary tumor before-chemotherapy should be included. Six guidelines recommend that the primary tumor post-chemotherapy (ASTRO[18], NCCN[21], ESMO[22], FMS[24-26], CSCO[27], CSTRO[28]) and the involved nodal regions before chemotherapy (SEOM[17], ASTRO[18], NCCN[21], ESMO[22], CSCO[27], CSTRO[28]) should be included. Four guidelines advise omission of elective nodal irradiation (ENI) (ASTRO[18], ARS[19,20], ESMO[22], FMS[24-26]). Others have no related information.

All applicable guidelines recommend PCI (25 Gy) in patients who have achieved response to initial therapy. PCI should be started 3-4 weeks after chemoradiotherapy (CRT) (n=3, CSCO[27], CSTRO[28], CMA[29]), within 60 days after completing of chemotherapy (n=1, FMS[24-26]), after initial therapy (n=2, SEOM[17], NCCN[21]), or no time period is specified (ASTRO[18], ARS[19,20], NICE[23], ESMO[22]). The recommendation to hippocampal-avoidance PCI (HA-PCI) is controversial (can be considered: NCCN[21], CSCO[27], CSTRO[28]; to be defined: ASTRO[18]; consider in clinical trial: ARS[19,20]; no benefit: ESMO[22]) (Table 3).

3.3.3. Stage IV (extensive disease)

For stage IV patients, five guidelines recommend ICI (atezolizumab or durvalumab) and chemotherapy, followed by maintenance ICI as first-line treatment in patients with good performance status (PS) (SEOM[17], NCCN[21], ESMO[22], CSCO[27], CSTRO[28]), while others have no related information. Consolidative TRT is advised in all guidelines for patients who responded to chemotherapy but have residual thoracic disease. TRT dose recommendations are summarized in Table 4. The recommendations about TRT in patients treated with chemo-ICI and afterwards maintenance ICI are not clear (Table 4)[30].

Six guidelines recommend PCI in patients with good response and good PS (SEOM[17], ESMO[22], CSCO[27], CMA[29], NICE[23], ARS[19,20]). The NCCN recommends that PCI may be considered[21]. The ASTRO suggests shared decision making for either PCI or magnetic resonance imaging (MRI) surveillance[18]. The ARS notes as well that if cranial MRI surveillance is available, PCI can be withheld[19,20]. The FMS[28] and the CSTRO[28] also recommend PCI if MRI surveillance is not convenient. Two guidelines recommend MRI surveillance regardless of PCI status (SEOM[17], NCCN[21]). All applicable guidelines advise whole-brain radiotherapy (WBRT) in patients with brain metastases (BM) (Table 4).

4. Discussion

Guidelines are very important to help clinicians treat patients properly. However, multiple guidelines exist and updates are regularly needed, which is burdensome for guideline committees. We compared the radiotherapy recommendations in 11 current SCLC guidelines from different countries and continents and found that most of the recommendations are similar, with some differences in controversial fields.

One possible reason for the existing differences is that methods of development (e.g. systematic vs. non-systematic literature review) for the guidelines differ, which might influence the recommendations. A systematic review of the literature ensures that studies are identified according to pre-specified criteria and that no studies are missed, but is also more time consuming. Additionally, committees use different methods to evaluate the SOE and specify the SOR, which might also influence the recommendations given. Furthermore, it can be confusing to readers. For example, the SEOM[17] and ESMO[22] classify the SOE into "I, II, III (IV, V)", while the FMS[24-26] and CSCO[27] use "1, 2, 3 (4) / I, II, III (not recommend/ against)" to describe the SOR. A more uniform way to report SOE and SOR is needed to avoid misunderstanding. The recommendation differences in controversial fields are discussed below.

4.1. SBRT in early stage SCLC

SBRT is considered for patients with very early stage SCLC in six guidelines, but the SOE is not very high. As it is the standard of care for inoperable early stage NSCLC[23,29], SBRT has often been extrapolated to early stage SCLC. *Verma et al.* reviewed 74 inoperable stage I (T1-2N0) patients with SBRT and found that SBRT together with chemotherapy (92% sequentially) resulted in appropriate outcome[5], adding that chemotherapy would improve overall survival (OS) (median OS, 31.4 vs. 14.3 months, $P = 0.02$)[6]. *Li et al.* conducted a phase II study to investigate the role of SBRT in 29 patients with limited stage-SCLC (LS-SCLC) and found that SBRT (40-45 Gy in 10 fractions) concurrent with chemotherapy was safe and effective[4]. A randomized phase II trial (NCT02738723) is ongoing, comparing SBRT and intensity modulated radiotherapy (IMRT) in LS-SCLC[31], which will hopefully provide more information. As SBRT can shorten the radiation courses, which could mitigate the risk of infecting SARS-CoV-2[32,33], we presume it would be suitable to try SBRT in selected early stage patients, especially in the current time when COVID-19 is prevalent.

4.2. TRT in resected stage I-IIA SCLC patients with pN1

The use of TRT in resected stage I-IIA SCLC patients with pN1 is controversial among guidelines, although the recommendations are sometimes based on the same study or even on retrospective studies (which are often not considered in clinical guidelines). SEOM[17] and NCCN[30] recommend TRT without providing the background literature. ARS gives a suggestion based on expert consensus[19]. CSTRO[28] advises TRT because a small retrospective study including a limited number of patients with N1 disease (pN1: n=20; cN1: n=10) showed that post-operative radiotherapy (PORT) prolonged OS in that subgroup[34]. CMA[29] gives a recommendation based on two studies (one based on the Surveillance, Epidemiology, and End Results [SEER] database, in which 241 patients underwent PORT[35], and the other based on the National Cancer Database [NCDB], in which 448 patients underwent PORT[36]). However, both studies showed that PORT was not significantly associated with survival in patients with pN1. CSCO[27] recommends this treatment because the NCDB study showed that the 5-year OS was numerically higher in the PORT group (33.3% vs. 27.7%, $P = 0.22$)[36]. However, the ASTRO[18] committee does not recommend radiotherapy based on the same study[36], as they claim that the benefit-to-harm ratio is likely even less advantageous for N0-1 disease than N2 disease.

4.3. TRT dose and timing

Most guidelines advise to start TRT at the first or second cycle of chemotherapy[37-40]. Either 45 Gy BID or 60-70 Gy QD is advised based on the CONVERT trial results (although the trial did not prove that 60-70 Gy QD was as effective as 45 Gy BID, in several guidelines except ESMO and FMS, the CONVERT results were interpreted as so that 60-70 Gy was also an option)[41]. CCO[16] advises starting TRT as early as possible based on committee consensus, while FMS[24-26] advises to start TRT within 30 days from the start of chemotherapy, because a meta-analysis showed that shorter SER (< 30 days) improved the 5-year OS by more than 20%.

Table 3
Recommendations of Guidelines: Stage IIB–IIIC (cT3–4, N0, M0; T1–4, N1–3, M0)*.

Guideline (version), online year	RT	RT dose	RT time	RT volume	PCI	PCI dose	PCI time
North America							
CCO (2018), 2018[1]	CCRT [Consensus]	45 Gy, BID / 40 Gy/15 fractions, QD / a biologically equivalent dose [Low-High]	As early as possible [Consensus]	NI	NA	NA	NA
ASTRO (2020), 2020[2]	CCRT	45 Gy, BID [Strong, High]; If infeasible: 60-70 Gy, QD [Conditional, Moderate]	1st /2nd ChT [Strong, Moderate]; If tumor shrinkage might decease RT toxicities: 3rd ChT	IFI [Strong, Moderate]; Primary tumor: post-ChT; Involved nodal regions: before ChT [Strong, Moderate];	Age < 70 years, PS 0-2, response: yes [Strong, High]; HA-PCI: yet to be defined; Limited PS, advanced age, preexisting neurocognitive conditions, significant comorbid conditions: shared decision making [Strong, Low]	25 Gy in 10 fractions [Strong, Moderate];	NI
ARS (2020), 2020[3,4]	CCRT	45 Gy, BID [↑, S]; If infeasible, 60-70 Gy QD [↑, S]	1st /2nd ChT [↑, S]	Not ENI [-, EC]	Yes [↑, S]; HA-PCI: consider in clinical trial [↓, L]; Quarterly MRI surveillance is also appropriate [↓, EO]	25 Gy in 10 fractions [↑, S]	NI
NCCN (2.2021), 2021[5]	CCRT	45 Gy, BID [Category 1]; Or 60-70 Gy QD	1st /2nd ChT [Category 1]	Primary tumor: post-ChT; Involved nodal regions: before ChT	Yes [Category 1]; HA-PCI: can be considered Impaired cognitive functioning or poor PS: no	25 Gy in 10 fractions	After initial therapy
Europe							

(*continued on next page*)

Table 3 (*continued*)

ESMO (2021), 2021[6]	PS 0-1: CCRT [A, I]; PS≥2: SCRT [B, V]	45 Gy, BID [A, I]	1st /2nd ChT [A, II]; If early RT is infeasible: 3rd ChT [B, II]	Primary tumor: post-ChT [B, II]; Involved nodal regions: before ChT [B, V]; ENI: omission [A, III]	Response and PS 0-1: yes [A, I]; PS 2: can be considered [B, III]; Frail/elder (> 70): shared decision making [C, V]; HA-PCI: no benefit	25 Gy in 10 fractions [A, I];	NI
NICE (2019), 2019[7]	CCRT [Offer]; Not well enough for CCRT: SCRT [Offer].	PS 0-1: BID [Offer]; If infeasible: QD [Offer];	1st /2nd ChT [Offer]	NI	PS 0-2: yes [Offer]; HA-PCI: NI	25 Gy in 10 fractions [Offer]	NI
FMS (2019), 2019[8-10]	CCRT; If infeasible: SCRT	45 Gy, BID [1, A1]	Within 30 days of the start of ChT [1, A1]	Primary tumor: post-ChT [2, A2]; With FDG-PET: IFI [3, C]; Doubt involvement of a particular lymph node station: IFI [3, C];	Yes: [1, A1]; HA-PCI: NI	25 Gy in 10 fractions [1, A1]	Within 60 days after completing the ChT [1, A1]
SEOM (2019), 2020[11]	CCRT [A, I]	45 Gy, BID / 60-70 Gy, QD [A, I]	1st /2nd ChT [A, I]	Primary tumor: before ChT; Involved nodal regions: before ChT	Response: Yes [A, I]; HA-PCI: NI	25 Gy in 10 fractions [A, I]	After chemoradiotherapy
China							
CSCO (2020), 2020[12]	PS 0-2: CCRT [I, category 1]; If infeasible: SCRT [I, category 1]; PS 3-4 caused by SCLC: ChT ± RT [I, category 2A]; PS 3-4 not caused by SCLC: BSC [I]	45 Gy, BID [NI]; Or 60-70 Gy QD.	1st /2nd ChT [NI]; If early RT is infeasible: After 2nd ChT [NI]	Primary tumor: post-ChT; Involved nodal regions: before ChT [NI]	Yes [II, category 1]; HA-PCI: yes if logistics feasible >65 years old, PS > 2, or with neurocognitive functioning impairment: no	25 Gy in 10 fractions	Within 3-4 weeks after chemoradiotherapy
CSTRO (2020), 2020[13]	PS 0-1: CCRT; PS 2: be cautious with CCRT; PS 3-4: SCRT, ChT	45 Gy, BID / 60-70 Gy, QD	1st /2nd ChT; Huge tumor, extensive lymph nodes metastasis, or	Primary tumor: post-ChT; Involved nodal regions: before ChT	Response: yes; HA-PCI: yes, if logistics feasible	25 Gy in 10 fractions	3-4 weeks after chemoradiotherapy

(*continued on next page*)

Table 3 (*continued*)

	alone, RT alone, individualized treatment, or BSC		obstructive atelectasis: after 2nd ChT; Start RT no less than the 3rd ChT;				
CMA (2019), 2019[14]	PS 0-2: CCRT [category 1]; if infeasible: SCRT; PS 3-4 caused by SCLC: SCRT/CCRT; PS 3-4 not caused by SCLC: BSC	45 Gy, BID or 60-70 Gy, QD	1st /2nd ChT;	NI	Response: yes [category 1]; HA-PCI: NI; > 65 years old, with a PS greater than 2, or have severe concomitant diseases, or have neurocognitive impairment: no	25 Gy in 10 fractions	3 weeks after chemoradiotherapy
Summary	All guidelines prefer CCRT	Both 45 Gy BID and 60-70 Gy QD are recommended; 45 Gy BID is specifically advised in ESMO and FMS	It is often recommended to start RT at 1st/2nd ChT	IFI is recommended	PCI is recommended, HA-PCI is controversial	The recommended PCI dose is 25 Gy	The timing of PCI is less consensus

* Consistent recommendations are colored as yellow ( ); less consensus as green ( ); inconsistent as turquoise ( ).

Abbreviations: BID, twice-daily radiotherapy; BSC, best supportive care; CCRT, concomitant chemoradiotherapy; ChT, chemotherapy; ENI, elective nodal irradiation; HA-PCI, hippocampal-avoidance PCI; IFI, involved field irradiation; NA, non-applicable; NI, no information; PCI, prophylactic cranial irradiation; PS, performance status; QD, once-daily radiotherapy; RT, radiotherapy; SCRT, sequential chemoradiotherapy.

Abbreviations for guidelines:

CCO, the Cancer Care Ontario's (CCO's) Lung Cancer Disease Site Group (DSG);

ASTRO, the American Society for Radiation Oncology;

ARS, the American Radium Society (ARS) Thoracic Appropriate Use Criteria Committee (AUC);

NCCN, the National Comprehensive Cancer Network;

ESMO, the European Society for Medical Oncology;

NICE, the National Institute for Health and Care Excellence;

FMS, Federatie Medisch Specialisten;

SEOM, the Spanish Society of Medical Oncology;

CSCO, the Chinese Society of Clinical Oncology;

CSTRO, the Chinese Society for Radiation Oncology;

CMA, the Chinese Medical Association.

Table 4
Recommendations of Guidelines: Stage IV (extensive disease)*.

Guideline (version), online year	No BM				BM
	First-line IMT + ChT	RT	PCI	Brain MRI surveillance	
North America					
CCO (2018), 2018[1]	NI	Low-volume extra-thoracic disease/residual intra-thoracic disease: yes [Moderate]; Dose: 30 Gy in 10 fractions, QD / 45 Gy in 15 fractions, QD / 45 Gy in 30 fractions, BID	NA	NA	NA
ASTRO (2020), 2020[2]	NA	Responese to ChT, residual thoracic tumor: yes [Strong, High]; RT dose: 30 Gy in 10 fractions, a higher dose might be considered [Conditional, Moderate]; RT time: after completing ChT [Strong, High]; Response to ChT and IMT: within 6-8 weeks.	Shared decision making [Strong, Moderate]; PCI dose: 25 Gy in 10 fractions or 20 Gy in 5 fractions [Strong, Moderate]	Shared decision making [Strong, Moderate]	NA
ARS (2020), 2020[3,4]	NA	Residual disease after ChT: yes [↑, S]; IMT+ ChT: yes [↑, M], after chemoimmunotherapy; RT dose: 30-54 Gy [↑, M]	Yes [↑, S]; If surveillance: no [↑, S]; PCI dose: 25 Gy in 10 fractions [↑, S]	Yes [↑, S]	WBRT [↑, S]; Dose: 30 Gy in 10 fractions [↑, S]; In selected patients: SRS [↑, M]
NCCN (2.2021), 2021[5]	Yes, atezolizumab / durvalumab	Yes; RT dose: 30 Gy in 10 fractions to 60 Gy in 30 fractions, or equivalent regimens; RT time: after chemoimmunotherapy, before or during maintenance IMT	Can be considered; PCI dose: 25 Gy in 10 fractions or shorter course (20 Gy in 5 fractions)	Yes	WBRT; Dose: 30 Gy in 10 fractions; In selected patients: SRS
Europe					
ESMO (2021), 2021[6]	PS 0-1: Atezolizumab / Durvalumab [A, I]	Response, PS 0-2: yes (30 Gy/10 fractions) [C, II]	< 75, response, PS 0-2: yes [B, II] Dose: 25 Gy in 10 fractions or 20 Gy in 5 fractions [B, II]; Can be followed-up with regular brain MRI: no [B, II]	Did not undergo PCI: yes [C, II]	NA
NICE (2019), 2019[7]	NI	Response: yes [Consider]	Response, PS 0-2: yes [Consider]	NI	NA
FMS (2019), 2019[8-10]	NI	Response, PS 0-1: yes (30 Gy/10 fractions) [NI]	No MRI surveillance: yes [NI]	Yes, quarterly [NI]	WBRT + ChT (not concurrently) [3, A2]
SEOM (2019), 2020[11]	Atezolizumab / Durvalumab [A, I]	Good response: yes [B, I]	Good response and PS: yes (25 Gy in 10 fractions) [B, I]; Elderly patients: be cautious; Patients at high risk of neurological sequelae (neuro-cognitive impairment or PS 3–4): no	Yes [B, I]	Symptomatic: WBRT (30 Gy) -> Systemic therapy; Asymptomatic: systemic therapy -> WBRT (30 Gy) [A, II]
China					
CSCO (2020), 2020[12]	PS 0-2 / PS 3-4 caused by SCLC: Atezolizumab [I, category 1A] / Durvalumab [III, category 1A]	Response: Yes [II, category 2A]; Dose: between 30Gy in 10 fractions and 60Gy in 30 fractions, or equivalent regimens in this range	Response: yes [II, category 2A]	NI	Symptomatic: WBRT-> IMT (Atezolizumab) + ChT [I, category 1A]; WBRT-> ChT [I, category 2A]; WBRT-> IMT (durvalumab) + ChT [III, category 1A]; Asymptomatic: IMT (Atezolizumab) + ChT -> WBRT [I, category 1A]; ChT -> WBRT [I, category 2A]; IMT (durvalumab) + ChT -> WBRT [III, category 1A]; WBRT dose: 30 Gy in 10 fractions; BM after PCI: SRS
CSTRO	Yes	Oligometastasis, response:yes;	Good PS or not convenient	Yes	WBRT (30 Gy in 10 fractions);

(*continued on next page*)

Table 4 (*continued*)

(2020), 2020[13]		Dose: between 30 Gy in 10 fractions and 60 Gy in 30 fractions;	for MRI surveillance: yes		Oligo BM: WBRT + SRS / SIB
CMA (2019), 2019[14]	NI	Good PS, response: Yes [category 2A]	Yes, with caution [category 2A].	NI	Symptomatic: WBRT -> ChT [category 2A]; Asymptomatic: ChT -> WBRT [category 2A];
Summary	IMT (atezolizumab /durvalumab) is recommended	Consolidative RT (30-60 Gy) is recommended; Timing of RT and IMT is controversial	PCI vs brain MRI surveillance is controversial		WBRT is recommended.

* Consistent recommendations are colored as yellow ( ); less consensus as green ( ); inconsistent as turquoise ( ).
Abbreviations: BID, twice-daily radiotherapy; BM, brain metastasis; ChT, chemotherapy; IMT, immunotherapy; MRI, magnetic resonance imaging; NA, non-applicable; NI, no information; PCI, prophylactic cranial irradiation; PS, performance status; QD, once-daily radiotherapy; RT, radiotherapy; SCLC, small cell lung cancer; SIB, simultaneous integrated boost; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.
Abbreviations for guidelines:
CCO, the Cancer Care Ontario's (CCO's) Lung Cancer Disease Site Group (DSG);
ASTRO, the American Society for Radiation Oncology;
ARS, the American Radium Society (ARS) Thoracic Appropriate Use Criteria Committee (AUC);
NCCN, the National Comprehensive Cancer Network;
ESMO, the European Society for Medical Oncology;
NICE, the National Institute for Health and Care Excellence;
FMS, Federatie Medisch Specialisten;
SEOM, the Spanish Society of Medical Oncology;
CSCO, the Chinese Society of Clinical Oncology;
CSTRO, the Chinese Society for Radiation Oncology;
CMA, the Chinese Medical Association.

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(RR = 0.62; 95% CI: 0.49, 0.80; $P = 0.0003$)[42], which was confirmed in an individual patient data meta-analysis[43].

4.4. TRT target volume

Most guidelines with information on this topic recommend that the primary tumor post-chemotherapy and the involved nodal regions before chemotherapy should be included, while ENI should be omitted. The SEOM[17] guideline emphasizes that the primary tumor before-chemotherapy should also be included. They cite the Cancer and Leukemia Group B (CALGB) 39808 trial[44]. However, residual primary tumor post-chemotherapy was included in this study and the reasons for the SEOM recommendation remain unclear.

4.5. PCI in resected stage I-IIA

FMS[24-26] gives a recommendation based on two studies (one retrospective study, n=95[45], and one non-randomized study, in which 36/104 patients received PCI[46]) showing that combination of surgery, chemotherapy, TRT, and PCI could achieve promising results in stages I and II[45,46], but the SOE and SOR are not high ([3, C]). CSCO[27] makes a recommendation [II, category 1] based on the meta-analysis of *Auperin et al*[47]. This study showed that PCI decreased BM and improved OS in patients with complete remission. However, the PCI benefit in the subgroup of resected stage I-IIA was not clear. CSCO[27] also noted that PCI benefit might be lower in patients with stage I because the BM incidence is relatively low (<10%)[48]. SEOM[17] does not recommend PCI because a meta-analysis showed that the BM incidence in patients with p-stage I was low (5-year BM incidence: 12%)[49]. ASTRO[18] does not recommend PCI in stage I because of the risk-benefit ratio consideration: Several studies have shown that the BM incidence is low and the OS benefit remains unestablished in this subgroup[49-51], while on the other hand, PCI might have negative effect on neurocognitive function[52] and quality of life[53]. ARS recommends PCI in patients who are at risk for being lost to follow-up [-, L][19,20], but states that the advice is controversial because the evidence is very limited[54,55]. In this field, the controversy between guidelines results from the lack of high quality evidence.

4.6. PCI in stage I-IIA without surgery

This remains controversial as there is a lack of high-level evidence. CSCO[27], SEOM[17], ASTRO[18], and ESMO[22] manage it the same as resected

stage I-IIA. ARS recommends PCI in patients who are at risk for being lost to follow-up based on experts opinion ([-, EO])[19,20]. CSTRO[28] suggests that this can be decided based on each patient's specific status and willingness. Others manage it the same as stage IIB-IIIC (NCCN[21], NICE[23], FMS[24-26], CMA[29]). The reasons are similar for controversial recommendations of HA-PCI. To date, the Dutch NCT01780675 trial [56] and the Spanish PREMER trial[57] have drawn conflicting conclusions. Other ongoing trials have been discussed extensively in another review[58]. More data are needed to define this issue.

4.7. Timing of PCI

This remains not very clear. The FMS[24-26] recommends PCI within 60 days after completion of chemotherapy based on two publications[47,59]. In the randomized clinical trial, the interval between end of chemotherapy and start of PCI was 46 days (0-318) in standard dose group vs. 42 days (3-271) in higher dose group[59]. The meta-analysis showed a trend ($P = 0.001$) that earlier administration of PCI after induction therapy (<4, 4-6, >6 months) could decrease BM risk without an effect on OS[47], but it didn't establish the precise optimal timing of PCI. The Chinese societies recommend starting PCI 3-4 weeks after CRT[27-29], but the evidence is unclear. SEOM[17] and NCCN[21] recommend applying PCI after initial therapy, but without a reference as well. Other guidelines do not specify the PCI timing, and timing remains a grey area.

4.8. PCI in ES-SCLC

Both PCI and cranial MRI surveillance are recommended in extensive stage-SCLC (ES-SCLC). The SEOM[17] and NCCN[21] recommend MRI surveillance regardless of PCI status. The different recommendations are mainly based on two randomized phase III trials[7,8], which have demonstrated contradictory OS results in patients with ES-SCLC. The EORTC trial showed that PCI reduced symptomatic BM incidence (HR, 0.27; 95% CI: 0.16, 0.44; $P < 0.001$; 1 year BM: 14.6% in the PCI group vs. 40.4% in the control group) and improved OS (1 year OS: 27.1% in the PCI group vs. 13.3% in the control group, $P = 0.003$)[7]. In contrast, the Japanese trial showed no OS improvement (HR, 0.27; 95% CI: 0.96, 1.68; $P = 0.094$) despite a reduction in BM incidence (1 year BM: 32.9% in the PCI group vs. 59.2% in the control group, $P < 0.0001$) [8]. Major differences in trial design (primary endpoint, MRI screening and follow-up) are probably the explanation for the differences in the outcomes. The NICE committee specified that the Japanese trial was not applicable for the UK because the UK has much less MRI scanners per million population than Japan (6 versus 52). Therefore, such a frequent MRI follow-up was impractical in the UK[60], as in many other countries worldwide. However, the EORTC trial was much more applicable for the UK since most of the study centers were in Europe and approximately half were in the UK[60]. Hence, in addition to the clinical benefits, committees also take cost-effectiveness and value-based measures into consideration. The accessibilities to facilities are different across nations or areas. This is another cause of the recommendation differences.

4.9. TRT and PCI with ICI

The rapid development of ICI has brought the treatment of ES-SCLC to a new era. Based on the IMpower 133 trial[12], the Food and Drug Administration (FDA) approved atezolizumab in combination with etoposide and carboplatin for the first-line treatment of ES-SCLC on March 18, 2019, followed by the European Medicines Agency (EMA) on September 6, 2019. Based on the CASPIAN trial[13], the FDA approved durvalumab in combination with etoposide and either cisplatin or carboplatin for the first-line treatment of ES-SCLC on March 27, 2020, followed by EMA on July 23, 2020. Therefore, guidelines recommend both atezolizumab and durvalumab in combination with chemotherapy as first-line treatment in ES-SCLC[17,22,30] except for the CSCO guideline, which recommends atezolizumab as level I SOR and durvalumab as level III of SOR since the Chinese National Medical Products Administration (NMPI) approved atezolizumab in February, 2020 , but has not approved durvalumab yet[27]. However, the combination of TRT and PCI in this new setting remains unclear because of the paucity of related data. In the IMpower 133 trial[12], patients with treated asymptomatic BM were eligible. PCI was allowed after completing the induction phase, but the detailed timing was not specified. Only 10.9% (44/403, 22 in each group) patients received PCI. In the CASPIAN trial[13], patients with asymptomatic or treated BM were eligible. PCI was allowed in the chemotherapy group but not in the two durvalumab arms. TRT was not allowed in both trials. Yet, the ASTRO committee recommends that TRT could be applied within 6-8 weeks after completing chemotherapy combined with ICI based on expert opinion[18]. The NCCN[21] advises that TRT could be considered after chemo-ICI, before or during maintenance ICI[30]. The ARS committee also suggests that TRT could be appropriate, but denotes that the optimal sequencing is lacking[20]. Hopefully, the ongoing NRG LU005 trial (atezolizumab in LS-SCLC) and NRG LU007 trial (atezolizumab in ES-SCLC)[61,62] will offer more experience in this issue.

In summary, despite the face that the developing methods can be different, most guidelines make similar radiotherapy recommendations, though the SOE and SOR can be slightly different. Some controversial areas exist, as discussed before. The differences seem to be due to a paucity of high quality evidence, evidence selection, certain evidence interpretation, cost-effective considerations, accessibility to facilities or drugs, etc.

The similarities between guidelines reflect the fact that much of the work by different organizations or societies is repeated and overlaps, which might be unnecessary. On the other hand, each guideline gives no information on certain aspects. For example, the ASTRO[18] and ESMO[22] guidelines do not cover WBRT for BM. That is, no single guideline is perfect and can guide clinicians throughout all different clinical problems/presentations. Therefore, we appeal for a better international collaboration to allow colleagues worldwide to collaborate more efficiently and avoid duplicating unnecessary work. Experts from all over the world could work together for one "global" guideline based on the current evidence and each society can adapt a specific version based on their own social development, and economic and facility status, with consideration of the potential impact of the guideline on the legal consequences in medical controversies. Endorsement[63] or joint guidelines[64] among multiple societies are good examples. This can save considerable energy and resources so that more efforts could be focused on making new progress, such as further investigating the controversial or unknown areas. Clinicians would also be able to stay abreast of guidelines and updates more efficiently.

5. Conclusion

The major radiotherapy principles are consistent across guidelines. This reveals that experts worldwide might be duplicating unnecessary work. We suggest better international collaboration to save energy and resources. More efforts should be devoted to solving the controversial or unknown problems.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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Author contributions

F.K., H.Z., D.R., and L.H. conceived this study. H.Z. and L.H. searched guidelines. H.Z. extracted the data, compared the guidelines, and analyzed the results. D.R. and L.H. supervised the whole process. H.Z., L.H. and D.R. draft the manuscript, F.K., X.H., D.Z., U.R. and L.Y. revised it.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2022.02.003.

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