European Respiratory Society guideline on various aspects of quality in lung cancer care

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Shareable abstract (@ERSpublications)
A multidisciplinary ERS Task Force panel including patient representatives created a clinical practice guideline on good quality in lung cancer care. Implementing the 13 consented recommendations can sustainably improve patient experiences and outcomes. https://bit.ly/3S3NsFQ

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Abstract

This European Respiratory Society guideline is dedicated to the provision of good quality recommendations in lung cancer care. All the clinical recommendations contained were based on a comprehensive systematic review and evidence syntheses based on eight PICO (Patients, Intervention, Comparison, Outcomes) questions. The evidence was appraised in compliance with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Evidence profiles and the GRADE Evidence to

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Decision frameworks were used to summarise results and to make the decision-making process transparent. A multidisciplinary Task Force panel of lung cancer experts formulated and consented the clinical recommendations following thorough discussions of the systematic review results. In particular, we have made recommendations relating to the following quality improvement measures deemed applicable to routine lung cancer care: 1) avoidance of delay in the diagnostic and therapeutic period, 2) integration of multidisciplinary teams and multidisciplinary consultations, 3) implementation of and adherence to lung cancer guidelines, 4) benefit of higher institutional/individual volume and advanced specialisation in lung cancer surgery and other procedures, 5) need for pathological confirmation of lesions in patients with pulmonary lesions and suspected lung cancer, and histological subtyping and molecular characterisation for actionable targets or response to treatment of confirmed lung cancers, 6) added value of early integration of palliative care teams or specialists, 7) advantage of integrating specific quality improvement measures, and 8) benefit of using patient decision tools. These recommendations should be reconsidered and updated, as appropriate, as new evidence becomes available.

Introduction

In 2020, lung cancer ranked first among all new cancer diagnoses worldwide and third within the European Union while remaining on top of cancer death and healthcare cost statistics [1–4]. Beyond these numbers, lung cancer is associated with a high rate of comorbidities and imposes an enormous burden on patients as well as their caregivers and professionals [5]. A previous European Respiratory Society (ERS) Task Force provided a first comprehensive snapshot of the management of lung cancer care throughout Europe. While substantial variation in terms of available infrastructure, implemented pathways and related outcomes was surveyed, underlying evidence on quality of lung cancer care appeared limited regarding evidence level, scope and comparability according to the concomitant narrative review [6]. Subsequently, an ERS statement on harmonised standards for lung cancer registration and lung cancer services in Europe was published [7].

Scope and objectives of the guideline

The objectives of our guideline are to present a robust and comprehensive evidence basis on relevant quality-defining aspects of lung cancer care and to present evidence-based recommendations promoting quality improvement. This document should set an initial standard for the provision of high-quality recommendations and concurrently a starting point for future quality improvement research in lung cancer care. Future periodic updates and adaptions will ensure that all relevant indexed literature in this field will be detected and appraised according to high methodological standards [8–10].

Specialists in lung cancer care who manage adult lung cancer patients are the target audience of this guideline. General internists, primary care physicians, emergency medicine clinicians, (lung) cancer nurses and other allied healthcare professionals as well as policy makers may also benefit from this guideline.

A plain language summary is available in the supplementary material.

Methods

Guideline development

This guideline was developed following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [8–10].

A multidisciplinary Task Force panel was constituted by the two Task Force co-chairs (T. Berghmans and T. Blum) with representatives from respiratory medicine, medical oncology, thoracic surgery, radiotherapy, pathology, radiology/nuclear medicine, palliative care and quality management. Further, a lung cancer nurse, a statistician, two librarians and representatives of the European Lung Foundation and their Patient Advisory Group were involved together with two ERS methodologists (T. Tonia and D. Rigau). The ERS lead methodologist (T. Tonia) ensured that all the methodological requirements were met, with assistance from the other methodologist. J. Chorostowska-Wynimko and R. Morgan were nominated as third Task Force co-chair and external co-lead methodologist, respectively, in May 2020 to facilitate the finalisation phase of this Task Force.

Panel meetings were held face-to-face and online *via* web conferences. A total of eight clinical questions were generated using the PICO (Patients, Intervention, Comparison, Outcomes) format and systematic reviews were conducted to answer these specific questions. The cut-off date for literature searches was 5 January 2021.

Disclosure of potential conflicts of interest

All Task Force panel members disclosed their conflicts of interest, according to ERS policies. None of the co-chairs or other panel members declared any conflicts of interest related to this guideline.

Systematic review

One experienced librarian from Université Libre de Bruxelles (Brussels, Belgium) designed and ran search strategies using MeSH (Medical Subject Headings) terms and key words for each clinical question, in collaboration with the methodology working group (T. Berghmans, T. Blum, D. Rigau and T. Tonia). The search focused on identifying randomised controlled trials (RCTs) and observational studies within the scope of the eight PICO questions. For inclusion, studies needed to provide lung cancer-specific data in lung cancer or mixed patient cohorts allowing comparison between intervention and control groups to establish the efficacy and safety of the intervention being studied. Eight separate searches in MEDLINE including update searches between April 2016 and January 2021 retrieved a total of 6281 articles; after removal of duplicates and exclusion of citations that did not meet the inclusion criteria, a total of 244 references were included in the initial evidence summaries. Data were extracted from RCTs and observational studies as described in supplementary material A. Observational studies were considered for inclusion in the evidence tables if RCTs were not available or of lower certainty of evidence. Meta-analyses on outcomes of interest were performed only if pooling of study patient cohorts was clinically meaningful. For aggregation methods, a fixed-effects method was used in case of absence of detection of heterogeneity of studies. Otherwise, random-effects models were applied.

If meta-analyses were not meaningful, the effect strength of studies was considered individually based on *our own individual four-stage evaluation scheme* (supplementary table A1).

Assessment of the level of evidence and degree of recommendations

The panel selected 12 outcomes of interest for each of the eight PICO question *a priori*. The importance of outcomes was rated on a 9-point scale (ranging from “not important” to “critical” for decision making) and only outcomes rated as important or critical for clinical decision making were included in the GRADE evidence profiles (supplementary table A3). We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations. GRADE methodology was used to assess the body of evidence at the outcome level rather than the study level, with risk of bias assessment at study level performed as described by Cochrane for RCTs [11] and GRADE for observational studies [12]. Some outcomes were addressed using a narrative format due to the lack of comparable studies.

The certainty of evidence was rated on four levels (high, moderate, low or very low) based on GRADE methodology [13]. The overall quality of evidence was then rated as the lowest of the critical outcomes, except where the evidence for all of the critical outcomes favoured the same alternative and where the quality of evidence for outcomes that are considered key to clinical decision took precedence [14]. GRADE evidence profiles were generated for each clinical question, followed by GRADE Evidence to Decisions frameworks integrating evidence assessments as well as the balance of benefits and harms, values and preferences, resource use, health equity, acceptability and feasibility as the basis for the recommendations. Recommendations are reported as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation. Of note, GRADE methodology allows making strong recommendations despite low or very low quality of evidence in certain defined constellations, so-called “paradigmatic situations”. Based on these formats, the panel formulated the clinical recommendations and decided on their strength by consensus or, if required, by voting. Following the GRADE approach, strong recommendations are worded as “we recommend”, while conditional recommendations are worded as “we suggest” [15].

Supplementary material A provides additional comprehensive information on 1) details of the methodology (including our own individual four-stage evaluation scheme and paradigmatic situations according to GRADE) as well as 2) search questions based on the PICO format, 3) rating of outcomes, 4) MEDLINE search strategies, 5) eligibility criteria for study inclusion and 6) PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowcharts for all eight PICO questions.

Recommendations

General remarks

For all eight PICO questions, our systematic literature searches retrieved very heterogeneous, sometimes limited pieces of evidence. As expected within the scope of this quality of care research, the evidence was

mainly based on observational studies while RCTs were rare. To overcome heterogeneity and to allow meaningful aggregation of studies, we formed subgroups within PICO questions, narrowing patient populations and/or interventions.

Supplementary material B presents detailed insights into the full GRADE outcome-based evidence rating and the evidence to recommendations process. This includes for each of the eight PICO questions: 1) a general summary of the evidence, 2) an outcome-based rating of the quality of evidence and GRADE evidence profiles in specific subgroups, and 3) GRADE Evidence to Decision frameworks.

This recommendations section of the main document provides the essence of this complex and extensive GRADE process. Table 1 offers an overview of the underlying evidence and the GRADE-based evidence rating per outcome sorted according to the eight PICO questions and their respective subgroups. Table 2 summarises the 13 formal, graded recommendations made within the guideline as well as implementation considerations and research needs which were all consented unanimously among the Task Force panellists. The following sections include a discussion of the available evidence as well as the expert and patient representative opinions of the Task Force panel for each of the eight PICO questions. These two pillars constitute the rationale for our GRADE-based recommendations.

PICO Question 1: In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (e.g. time from diagnosis to treatment)?

ERS recommendation

1) *In patients with lung cancer, we suggest minimising delay in initiation of first treatment.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

Remark: Evaluation should be complete before proceeding to any definitive treatment. Minimising delay in initial evaluation of the patient and specialist referral may also help to improve outcomes in lung cancer patients.

Problem

Early diagnosis and treatment of lung cancer is central to improve outcomes. Yet, lung cancer mortality is still high due to lack or late onset of symptoms as well as delayed presentation of patients to primary and secondary care. Delays may be contributed to by patients, primary and/or secondary care professionals as well as other factors [18].

Summary of evidence and overall quality of evidence

Due to substantial heterogeneity in the body of evidence relating to applied time intervals, we included only studies investigating treatment interval (time from date of diagnosis to date of treatment start) as intervention and selected 65 observational studies and two RCTs out of the 1791 initially identified abstracts accordingly [19–85]. To allow clinically meaningful pooling of data, we formed six subgroups: 1) non-small cell lung cancer (NSCLC), stage I/II, surgery; 2) NSCLC, stage I/II, all treatment modalities; 3) NSCLC, stage III, all treatment modalities; 4) NSCLC, stage I–IV, all treatment modalities; 5) anaplastic lymphoma kinase (ALK)-positive NSCLC, stage IIIB/IV, ALK tyrosine kinase inhibitor; and 6) small cell lung cancer (SCLC), all stages, all treatment modalities. From our predefined critical or important outcomes of interest, the following were addressed in the included studies: *overall survival*, *30-day mortality* and *90-day mortality* as well as *accuracy of staging*. The overall quality of evidence was rated as very low.

Desirable effects

Benefits of achieving shorter treatment intervals differed among the predefined subgroups. Patients with lung cancer subtypes stage I/II NSCLC with surgical resection (HR 0.893, 95% CI 0.847–0.943) and any tumour-specific treatment (HR 0.734, 95% CI 0.642–0.893) as well as ALK-positive stage IIIB/IV NSCLC (HR 0.49, 95% CI 0.27–0.88) who did not delay care had an increase in overall survival. With increasing stage or histological aggressiveness of tumours, analyses no longer detected any definite impact (*i.e.* stage III NSCLC). 30-day mortality as a short-term outcome was improved in the shorter treatment interval cohorts. While there may be an effect on 90-day mortality and accuracy of staging, the evidence was very uncertain.

Undesirable effects

In SCLC and stage IV NSCLC patients, shorter waiting times may not improve overall survival; however, the evidence is uncertain. Despite adjustments for stage in these studies, we assume other factors

TABLE 1 Summary of the underlying available evidence and the GRADE-based evidence rating per outcome sorted according to the eight PICO questions and their respective subgroups

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
PICO 1: In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (*e.g.* time from diagnosis to treatment)?			
Subgroup 1: NSCLC, stage I/II, surgical resection, treatment interval with shorter waiting times (*versus* longer waiting times)			
Overall survival	8 OBS (341 915 patients)	Meta: 7 (244 924 patients); HR 0.89, 95% CI 0.85–0.94 →shorter waiting times	Very low ⊕○○○
30-day mortality	2 OBS (32 006 patients)	Meta: 2 (32 006 patients); OR 0.81, 95% CI 0.71–0.93 →shorter waiting times	Very low ⊕○○○
90-day mortality	1 OBS (4984 patients)	1 (4984 patients); OR 0.80, 95% CI 0.62–1.03 →shorter waiting times	Very low ⊕○○○
Accuracy of staging	4 OBS (33 649 patients)	S: 1 (27 022 patients); T: 3 OBS (6627 patients) →shorter waiting times	Very low ⊕○○○
Subgroup 2: NSCLC, stage I/II, all treatment modalities, treatment interval with shorter waiting times (*versus* longer waiting times)			
Overall survival	8 OBS (670 006 patients)	Meta: 4 (132 673 patients); HR 0.73, 95% CI 0.64–0.84 →shorter waiting times	Very low ⊕○○○
Subgroup 3: NSCLC, stage III, all treatment modalities, treatment interval with shorter waiting times (*versus* longer waiting times)			
Overall survival	6 OBS (48 693 patients)	Meta: 4 (44 163 patients); HR 1.00, 95% CI 0.84–1.18 →shorter waiting times	Very low ⊕○○○
Subgroup 4: NSCLC, stage IV, all treatment modalities, treatment interval with shorter waiting times (*versus* longer waiting times)			
Overall survival	5 OBS (37 306 patients)	Meta: 2 (24 289 patients); HR 1.14, 95% CI 0.93–1.40 →longer waiting times	Very low ⊕○○○
Subgroup 5: ALK-positive NSCLC, stage IIIB/IV, ALK-TKI, treatment interval with shorter waiting times (*versus* longer waiting times)			
Overall survival	1 OBS (442 patients)	1 (442 patients); HR 0.49, 95% CI 0.27–0.88 →shorter waiting times	Very low ⊕○○○
Subgroup 6: SCLC, all stages, all treatment modalities, treatment interval with shorter waiting times (*versus* longer waiting times)			
Overall survival	2 OBS (67 933 patients)	L: 2 (67 933 patients) →longer waiting times	Very low ⊕○○○
PICO 2: In patients with lung cancer (or those suspected of having lung cancer), should a multidisciplinary team (MDT) or certain disciplines be involved during lung cancer care rather than no involvement of an MDT or certain disciplines?			
Subgroup 1: All lung cancer, all stages, all treatment modalities, MDT involvement (*versus* no MDT involvement)			
Overall survival	11 OBS (43 118 patients)	Meta: 4 OBS (9916 patients); HR 0.62, 95% CI 0.58–0.66 →MDT involvement	Very low ⊕○○○
Accuracy of staging	4 OBS (30 052 patients)	L: 1 (988 patients); M: 1 (3855 patients); S: 1 (593 patients); T: 1 (24 616 patients) →MDT involvement	Very low ⊕○○○
Pathological confirmation	2 OBS (4043 patients)	Meta: 2 (4043 patients); OR 2.42, 95% CI 1.75–3.35 →MDT involvement	Very low ⊕○○○
Receipt of curative treatment	6 OBS (32 998 patients)	Meta: 4 (7789 patients); OR 1.88, 95% CI 1.15–3.05 →MDT involvement	Very low ⊕○○○
Receipt of any tumour-specific treatment	5 OBS (30 866 patients)	Meta: 2 (4669 patients); OR 2.70, 95% CI 2.35–3.12 →MDT involvement	Very low ⊕○○○
Quality of life	1 RCT (88 patients)	T: 1 (88 patients) →MDT involvement	Moderate ⊕⊕⊕○
Patient satisfaction	1 RCT (88 patients)	T: 1 (88 patients) →MDT involvement	Moderate ⊕⊕⊕○

Continued

TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
Subgroup 2: NSCLC, all stages, all treatment modalities, MDT involvement (*versus* no MDT involvement)			
Overall survival	3 OBS (144 014 patients)	Meta: 3 (144 014 patients); HR 0.76, 95% CI 0.61–0.94 →MDT involvement	Very low ⊕○○○
30-day mortality	1 OBS (1222 patients)	1 (1222 patients); OR 1.23, 95% CI 0.47–3.20 →no MDT involvement	Very low ⊕○○○
Accuracy of staging	1 OBS (1222 patients)	1 (1222 patients); OR 3.56, 95% CI 2.49–5.10 →MDT involvement	Very low ⊕○○○
Receipt of curative treatment	2 OBS (1356 patients)	Meta: 2 (1356 patients); OR 1.26, 95% CI 1.00–1.59 →MDT involvement	Very low ⊕○○○
Subgroup 3: NSCLC, all stages, surgical resection, MDT involvement (*versus* no MDT involvement)			
Overall survival	3 OBS (2375 patients)	Meta: 2 (1555 patients); HR 0.77, 95% CI 0.50–1.15 →MDT involvement	Very low ⊕○○○
30-day mortality	2 OBS (1060 patients)	L: 1 (240 patients); T: 1 (820 patients) →MDT involvement	Very low ⊕○○○
Morbidity	1 OBS (820 patients)	1 (820 patients); OR 1.00, 95% CI 0.57–1.77 →MDT involvement	Very low ⊕○○○
Accuracy of staging	1 OBS (277 patients)	1 (277 patients); OR 8.09, 95% CI 4.07–16.08 →MDT involvement	Very low ⊕○○○
Pathological confirmation	1 OBS (1278 patients)	1 (1278 patients); OR 1.8, 95% CI 1.55–2.09 →MDT involvement	Very low ⊕○○○
Receipt of curative treatment	3 OBS (48 033 patients)	Meta: 2 (1418 patients); OR 2.55, 95% CI 1.92–3.40 →MDT involvement	Very low ⊕○○○
Receipt of any tumour-specific treatment	1 OBS (140 patients)	1 (140 patients); OR 8.86, 95% CI 3.75–20.96 →MDT involvement	Very low ⊕○○○
Subgroup 4: NSCLC, stage III/IV, all treatment modalities, MDT involvement (*versus* no MDT involvement)			
Overall survival	4 OBS (965 patients)	Meta: 3 (722 patients); HR 0.75, 95% CI 0.62–0.90 →MDT involvement	Very low ⊕○○○
Accuracy of staging	2 OBS (352 patients)	Meta: 2 (352 patients); OR 2.06, 95% CI 1.37–3.10 →MDT involvement	Very low ⊕○○○
Receipt of curative treatment	1 OBS (98 patients)	1 (98 patients); OR 1.68, 95% CI 0.20–14.33 →MDT involvement	Very low ⊕○○○
Receipt of any tumour-specific treatment	2 OBS (341 patients)	Meta: 2 (341 patients); OR 1.67, 95% CI 1.05–2.66 →MDT involvement	Very low ⊕○○○
PICO 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOPs) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or SOPs?			
Subgroup 1: All lung cancer, all stages, all treatment modalities, guideline implementation (*versus* no guideline implementation)			
Overall survival	3 OBS (>38 661 patients)	M: 1 (38 661 patients); S: 1 (no figures); T: 1 (no figures) →guideline implementation	Very low ⊕○○○
30-day mortality	2 OBS (>38 661 patients)	L: 2 (>38 661 patients) →guideline implementation	Very low ⊕○○○

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TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
Accuracy of staging	1 OBS (38 661 patients)	L: 1 (38 661 patients) →guideline implementation	Very low ⊕◯◯◯
Receipt of curative treatment	1 OBS (38 661 patients)	T: 1 (38 661 patients) →guideline implementation	Very low ⊕◯◯◯
Receipt of any tumour-specific treatment	1 OBS (38 661 patients)	L: 1 (38 661 patients) →guideline implementation	Very low ⊕◯◯◯
Subgroup 2: NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies, guideline adherence (*versus* no guideline adherence)			
Overall survival	5 OBS (835 464 patients)	L–T depending on guideline recommendations: 5 (667 861 patients) →guideline adherence *versus* 1 (single subgroup: 167 603 patients); HR 1.25, 95% CI 1.09–1.30 →no guideline adherence	Very low ⊕◯◯◯
30-day mortality	2 OBS (1662 patients)	L: 1 (916 patients); T: 1 (746 patients) →guideline adherence	Very low ⊕◯◯◯
Morbidity	1 OBS (916 patients)	1 (916 patients); OR 0.8, 95% CI 0.4–1.4 →guideline adherence	Very low ⊕◯◯◯
Subgroup 3: All lung cancer, all stages, all treatment modalities, guideline adherence (*versus* no guideline adherence)			
Overall survival	2 OBS (43 131 patients)	L: 2 (43 131 patients) →guideline adherence	Very low ⊕◯◯◯
Subgroup 4: NSCLC, unresectable stage III, chemo- and/or radiotherapy, guideline adherence (*versus* no guideline adherence)			
Overall survival	1 OBS (45 825 patients)	1 (45 825 patients); HR 0.70, 95% CI 0.68–0.72 →guideline adherence	Low ⊕⊕◯◯
Subgroup 5: NSCLC, all stages, chemotherapy, guideline adherence (*versus* no guideline adherence)			
Overall survival	2 OBS (2753 patients)	T: 2 (2753 patients) →guideline adherence	Very low ⊕◯◯◯
Subgroup 6: SCLC, all stages, all treatment modalities, guideline adherence (*versus* no guideline adherence)			
Overall survival	1 OBS (404 patients)	1 (404 patients); L: 5/6 recommendations; T: 1/6 recommendations →guideline adherence	Very low ⊕◯◯◯
PICO 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialisation for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialisation for these procedures?			
Subgroup 1: All lung cancer, all stages, higher hospital volume of surgical resections (*versus* lower hospital volume)			
Overall survival	18 OBS (448 402 patients)	L: 12 (275 995 patients); M: 3 (57 643 patients); T: 3 (154 764 patients) →higher hospital volume	Very low ⊕◯◯◯
In-house mortality	12 OBS (434 948 patients)	L: 9 (388 079 patients); S: 2 (26 731 patients); T: 1 (20 138 patients) →higher hospital volume	Very low ⊕◯◯◯

Continued

TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
30-day mortality	31 OBS (1 745 923 patients)	L: 19 (965 608 patients); M: 4 (364 835 patients); S: 5 (384 345 patients); T: 3 (31 135 patients) →higher hospital volume	Very low ⊕○○○
60-day mortality	2 OBS (42 838 patients)	L: 1 (2084 patients); M: 1 (40 754 patients) →higher hospital volume	Very low ⊕○○○
90-day mortality	6 OBS (600 425 patients)	L: 4 (457 203 patients); M: 1 (139 802 patients); S: 1 (3420 patients) →higher hospital volume	Very low ⊕○○○
Morbidity	7 OBS (75 972 patients)	Due to heterogeneity see supplementary material B for details →higher hospital volume	Very low ⊕○○○
Receipt of curative treatment	1 OBS (1591 patients)	L: 1 (1591 patients) →higher hospital volume	Low ⊕⊕○○
Subgroup 2: All lung cancer, all stages, better hospital specialisation in surgical resections (*versus* less hospital specialisation)			
Overall survival	8 OBS (95 099 patients)	L: 4 (53 563 patients); M: 3 (39 945 patients); T: 1 (1591 patients) →better hospital specialisation	Very low ⊕○○○
In-house mortality	3 OBS (185 454 patients)	S: 2 (122 826 patients); T: 1 (62 628 patients) →better hospital specialisation	Very low ⊕○○○
30-day mortality	11 OBS (431 489 patients)	L: 6 (364 796 patients); M: 3 (49 686 patients); T: 2 (17 007 patients) →better hospital specialisation	Very low ⊕○○○
90-day mortality	3 OBS (349 685 patients)	L: 3 (349 685 patients) →better hospital specialisation	Very low ⊕○○○
Morbidity	1 OBS (13 735 patients)	L: 1 (13 735 patients) →better hospital specialisation	Low ⊕⊕○○
Accuracy of staging	1 OBS (40 090 patients)	L: 1 (40 090 patients) →better hospital specialisation	Very low ⊕○○○
Receipt of curative treatment	1 OBS (1591 patients)	L: 1 (1591 patients); OR 1.72, 95% CI 1.06–2.80 →better hospital specialisation	Very low ⊕○○○
Subgroup 3: All lung cancer, all stages, higher surgeon volume of surgical resections (*versus* lower surgeon volume)			
Overall survival	2 OBS (2950 patients)	L: 2 (2950 patients) →higher surgeon volume	Low ⊕⊕○○
In-house mortality	2 OBS (8869 patients)	L: 1 (4841 patients); T: 1 (4028 patients) →higher surgeon volume	Very low ⊕○○○
30-day mortality	4 OBS (53 981 patients)	L: 2 (9249 patients); M: 1 (24 092 patients); T: 1 (20 640 patients) →higher surgeon volume	Very low ⊕○○○
Morbidity	1 OBS (2295 patients)	Due to heterogeneity see supplementary material B for details →higher surgeon volume	Very low ⊕○○○

Continued

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TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
Subgroup 4: All lung cancer, all stages, better surgeon specialisation in surgical resections (*versus* less surgeon specialisation)			
Overall survival	3 OBS (21 576 patients)	L: 1 (19 745 patients); T: 2 (1831 patients) →better surgeon specialisation	Very low ⊕○○○
In-house mortality	3 OBS (224 056 patients)	L: 3 (224 056 patients) →better surgeon specialisation	Very low ⊕○○○
30-day mortality	4 OBS (266 488 patients)	L: 2 (45 290 patients); M: 1 (9579 patients); S: 1 (211 619 patients) →better surgeon specialisation	Very low ⊕○○○
Accuracy of staging	1 OBS (222 233 patients)	L: 1 (222 233 patients) →better surgeon specialisation	Low ⊕⊕○○
Receipt of curative treatment	2 OBS (4482 patients)	L: 1 (2891 patients); T: 1 (1591 patients) →better surgeon specialisation	Very low ⊕○○○
Subgroup 5a–i: Hospital volume of procedures other than surgical resection			
Subgroup 5a: All lung cancer, all stages, higher hospital volume of diagnostic bronchoscopies including EBUS (versus *lower hospital volume)*			
7-day mortality	1 OBS (77 755 patients)	L: 1 (77 755 patients) →higher hospital volume	Very low ⊕○○○
15-day mortality	1 OBS (77 755 patients)	L: 1 (77 755 patients) →higher hospital volume	Low ⊕⊕○○
30-day mortality	1 OBS (77 755 patients)	L: 1 (77 755 patients) →higher hospital volume	Low ⊕⊕○○
Morbidity	1 OBS (77 755 patients)	T: 1 (77 755 patients) →higher hospital volume	Very low ⊕○○○
Pathological confirmation	1 OBS (891 patients)	T: 1 (891 patients) →higher hospital volume	Very low ⊕○○○
Subgroup 5b: All lung cancer, all stages, higher hospital volume of pathological lung cancer diagnostics (versus *lower hospital volume)*			
Pathological confirmation	1 OBS (89 409 patients)	L: 1 (89 409 patients) →higher hospital volume	Low ⊕⊕○○
Subgroup 5c: NSCLC, stage II/IIIA, higher hospital volume of chemoradiotherapy (versus *lower volume)*			
Overall survival	2 OBS (734 patients)	L: 2 (734 patients) →higher hospital volume	Very low ⊕○○○
Progression-free survival	1 OBS (495 patients)	M: 1 (495 patients); HR 0.85, 95% CI 0.68–1.06 →higher hospital volume	Very low ⊕○○○
Subgroup 5d: NSCLC, stage IIIA, higher hospital volume of different treatment modalities (versus *lower volume)*			
Overall survival	1 OBS (83 673 patients)	L: 1 (83 673 patients) →higher hospital volume	Low ⊕⊕○○
Receipt of curative treatment	1 OBS (83 673 patients)	L: 1 (83 673 patients) →higher hospital volume	Low ⊕⊕○○
Subgroup 5e: All lung cancer, stage III/IV, higher hospital volumes of systemic therapies (versus *lower volume)*			
30-day mortality	1 OBS (26 277 patients)	T: 1 (26 277 patients) →higher hospital volume	Very low ⊕○○○
Subgroup 5f: NSCLC, stage IV, higher hospital volume of different treatment modalities (versus *lower volume)*			
Overall survival	1 OBS (338 445 patients)	L: 1 (338 445 patients) →higher hospital volume	Low ⊕⊕○○

Continued

TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
Receipt of any tumour-specific treatment	1 OBS (338 445 patients)	L: 1 (338 445 patients) →higher hospital volume	Low ⊕⊕◯◯
Subgroup 5g: NSCLC, all stages, higher hospital volume of different treatment modalities (versus *lower volume*)			
Receipt of curative treatment	1 OBS (43 544 patients)	L: 1 (43 544 patients) →higher hospital volume	Low ⊕⊕◯◯
Subgroup 5h: All lung cancer, all stages, higher hospital volume of different treatment modalities (versus *lower volume*)			
Overall survival	1 OBS (9235 patients)	L: 1 (9235 patients) →higher hospital volume	Low ⊕⊕◯◯
Subgroup 5i: All lung cancer, all stages, higher hospital volume of ICU-treated lung cancer patients (versus *lower volume*)			
30-day mortality	1 OBS (449 patients)	L: 1 (449 patients) →higher hospital volume	Very low ⊕◯◯◯
180-day mortality	1 OBS (449 patients)	L: 1 (449 patients) →higher hospital volume	Very low ⊕◯◯◯
Subgroup 6a and b: Hospital specialisation in procedures other than surgical resection			
Subgroup 6a: All lung cancer, all stages, better hospital specialisation in pathological lung cancer diagnostics (versus *less specialisation*)			
Pathological confirmation	1 OBS (89 409 patients)	T: 1 (89 409 patients) →better hospital specialisation	Very low ⊕◯◯◯
Subgroup 6b: NSCLC, all stages, better hospital specialisation in different treatment modalities (versus *less specialisation*)			
Receipt of curative treatment	1 OBS (43 544 patients)	L: 1 (43 544 patients) →better hospital specialisation	Low ⊕⊕◯◯
PICO 5: In lung cancer patients (or those suspected of having lung cancer), should pathological confirmation of tumours or subtyping of lung cancers be obtained rather than no pathological confirmation of tumours or subtyping of lung cancers?			
PICO 5a: Should pathological confirmation of tumours be obtained in lung cancer patients?			
Subgroup 1: All lung cancer, all stages, all treatment modalities, pathological confirmation (*versus* no pathological confirmation)			
Overall survival	3 OBS (143 410 patients)	L: 2 (6417 patients); L, M, S, T: 1 depending on subgroup (143 410 patients) →pathological confirmation	Very low ⊕◯◯◯
Receipt of any tumour-specific treatment	1 OBS (5906 patients)	L: 1 (5906 patients) →pathological confirmation	Low ⊕⊕◯◯
Subgroup 2: NSCLC, stage I/II, stereotactic body radiation, pathological confirmation (*versus* no pathological confirmation)			
Overall survival	4 OBS (481 patients)	Meta: 1 (481 patients); HR 1.28, 95% CI 0.59–1.85 →no pathological confirmation	Very low ⊕◯◯◯
Progression-free survival	1 OBS (165 patients)	1 (165 patients); HR 1.39, 95% CI 0.80–2.42 →no pathological confirmation	Very low ⊕◯◯◯
PICO 5b: Should histological subtyping of lung cancers be obtained in lung cancer patients? No systematic review performed due to limited direct evidence			
PICO 5c: Should molecular characterisation of lung cancers for actionable targets or response to treatment be obtained in lung cancer patients? No systematic review performed due to limited direct evidence			

Continued

TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
PICO 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?			
All lung cancer, all stages, all treatment modalities, early palliative care integration (*versus* no early palliative care integration)			
Overall survival	2 RCT (642 patients)	Meta: 2 (642 patients); HR 0.72, 95% CI 0.55–0.96 →early palliative care integration	Very low ⊕○○○
Receipt of any tumour-specific treatment	1 OBS based on RCT (151 patients)	1 (151 patients); first-line CT: OR 0.68, 95% CI 0.34–1.36; second-line CT: OR 0.92, 95% CI 0.45–1.87 →no early palliative care integration third-line CT: OR 1.19, 95% CI 0.51–2.78; fourth-line CT: OR 1.38, 95% CI 0.54–3.51 →early palliative care integration	Very low ⊕○○○
Quality of life	20 RCT, 2 non-RCT (1747 patients)	M: 1 (150 patients); S: 3 (359 patients); T: 18 (1238 patients) →early palliative care integration	Very low ⊕○○○
Patient satisfaction	4 RCT (at least 101 lung cancer patients; no lung cancer-specific data in three studies)	T: 4 (at least 101 lung cancer patients) →early palliative care integration	Very low ⊕○○○
PICO 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods?			
Subgroup 1: All lung cancer, all stages, all treatment modalities, application of cancer registries and quality indicators (*versus* no application)			
Overall survival	4 OBS (191 693 patients)	L: 2 (52 435 patients); T: 2 (139 258 patients) →application of cancer registries and quality indicators	Very low ⊕○○○
30-day-mortality	1 OBS (52 435 patients)	L: 1 (52 435 patients) →application of cancer registries and quality indicators	Very low ⊕○○○
Accuracy of staging	2 OBS (50 910 patients)	L: 2 (50 910 patients) →application of cancer registries and quality indicators	Very low ⊕○○○
Pathological confirmation	1 OBS (>140 000 patients)	M: 1 (>140 000 patients) →application of cancer registries and quality indicators	Very low ⊕○○○
Receipt of curative treatment	3 OBS (>231 096 patients)	S: 3 (>231 096 patients) →application of cancer registries and quality indicators	Very low ⊕○○○
Receipt of any tumour-specific treatment	3 OBS (>178 661 patients)	L: 3 (>178 661 patients) →application of cancer registries and quality indicators	Very low ⊕○○○
Subgroup 2: All lung cancer, all stages, all treatment modalities, application of specialised lung cancer services (*versus* no application)			
Overall survival	3 OBS (296 548 patients)	L: 3 (296 548 patients) →application of specialised lung cancer services	Very low ⊕○○○
Receipt of curative treatment	1 OBS (33 312 patients)	L: 1 (33 312 patients) →application of specialised lung cancer services	Low ⊕⊕○○

Continued

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TABLE 1 Continued

PICO question, PICO subgroups and *outcomes* per subgroup	Total number and type[#] of included studies (total number of patients) per outcome	Effect strength[¶] and effect direction[+] per outcome	Quality of evidence per outcome
Subgroup 3: All lung cancer, all stages, all treatment modalities, application of individual quality improvement measures (*versus* no application)			
Overall survival	1 OBS (1898 patients)	1 (1898 patients); HR 0.80, 95% CI 0.70–0.90 →application of individual quality improvement measures	Very low ⊕○○○
30-day mortality	1 OBS (2566 patients)	1 (2566 patients); OR 0.85, 95% CI 0.58–1.23 →application of individual quality improvement measures	Very low ⊕○○○
60-day mortality	1 OBS (2566 patients)	1 (2566 patients); OR 0.74, 95% CI 0.54–1.01 →application of individual quality improvement measures	Very low ⊕○○○
90-day mortality	1 OBS (2566 patients)	1 (2566 patients); OR 0.82, 95% CI 0.62–1.09 →application of individual quality improvement measures	Very low ⊕○○○
Accuracy of staging	2 OBS (4477 patients)	Meta: 2 (4477 patients); OR 1.47, 95% CI 1.10–1.96 →application of individual quality improvement measures	Very low ⊕○○○
Pathological confirmation	1 OBS (1896 patients)	1 (1896 patients); OR 1.19, 95% CI 0.97–1.47 →application of individual quality improvement measures	Very low ⊕○○○
Receipt of curative treatment	1 OBS (1911 patients)	1 (1911 patients); OR 1.04, 95% CI 0.77–1.40 →application of individual quality improvement measures	Very low ⊕○○○
Receipt of any tumour-specific treatment	1 OBS (1911 patients)	1 (1911 patients); OR 1.31, 95% CI 1.05–1.63 →application of individual quality improvement measures	Very low ⊕○○○
Subgroup 4: All lung cancer, all stages, all treatment modalities, application of audits/quality indicator systems (*versus* no application)			
30-day mortality	3 OBS (4739 patients)	L: 1 (202 patients); S: 2 (4537 patients) →application of audit/quality indicator systems	Very low ⊕○○○
Morbidity	2 OBS (20 335 patients)	L: 1 (778 patients); T: 1 (19 557 patients) →application of audit/quality indicator systems	Very low ⊕○○○
PICO 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?			
All lung cancer, all stages, all treatment modalities, involvement of patient decision tools (*versus* no involvement of patient decision tools)			
Patient satisfaction	5 RCT (233 patients)	S: 1 (109 patients); T: 4 (124 patients) →involvement of patient decision tool	Very low ⊕○○○

NSCLC: non-small cell lung cancer; ALK: anaplastic lymphoma kinase; TKI: tyrosine kinase inhibitor; SCLC: small cell lung cancer; ICU: intensive care unit; CT: computed tomography. [#]: study types: OBS: observational study; RCT: randomised controlled trial. [¶]: effect strength: for single studies, meta-analyses (Meta) or aggregation based on our own individual four-stage evaluation scheme in studies ineligible for meta-analysis (L/M/S/T: large/moderate/small/trivial effect; supplementary material A). [+]: effect direction: arrow indicates whether the observed effect favours the implementation of a specific quality improvement measure or no implementation of a specific quality improvement measure. All PICO questions were developed *a priori*.

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TABLE 2 Summary of recommendations in this guideline as well as specific implementation considerations and research needs

Quality improvement measure (*versus* control)	Recommendation	Strength	Overall quality of evidence	Specific implementation considerations and research needs (international/national/regional level)
PICO 1: In patients with lung cancer (or those suspected of having lung cancer), should shorter rather than longer cancer care time intervals be used (*e.g.* time from diagnosis to treatment)?				
Shorter treatment interval (*versus* longer treatment interval)	*1) In patients with lung cancer, we suggest minimising delay in initiation of first treatment.* Remark: Evaluation should be complete before proceeding to any definitive treatment. Minimising delay in initial evaluation of the patient and specialist referral may also help to improve outcomes in lung cancer patients.	Conditional	Very low	Creation of a comprehensive data basis on waiting times: • Acquisition of waiting time threshold benchmarks: prospective multicentric observational studies among specialised lung cancer service networks assessing waiting times and perceived factors for delay • Depiction of general care situation: retrospective/prospective population-based observational studies among clinical lung cancer registries assessing waiting times • Survey-based assessment of patient preferences/behavioural patterns Definition and consensus building of standardised waiting time thresholds: • Preferably pan-European consensus meeting of dedicated European societies and national representatives Monitoring and optimisation initiatives: • Periodical monitoring of waiting times and, if needed, adaption of waiting time thresholds • Coordinated optimisation initiatives with mutual knowledge exchange • Thorough exploration of the putative effect of longer waiting times resulting in better survival in advanced lung cancer
PICO 2: In patients with lung cancer (or those suspected of having lung cancer), should a multidisciplinary team (MDT) or certain disciplines be involved during lung cancer care rather than no involvement of an MDT or certain disciplines?				
Involvement of MDT (*versus* no involvement of MDT)	*2) We suggest the integration of MDTs and/or multidisciplinary consultation in the management of patients with (suspected) lung cancer.* Remark: We acknowledge that MDTs are already implemented broadly in lung cancer care, yet to achieve good integration, we see the need for better implementation of multidisciplinary teamwork throughout the lung cancer pathway as well as for frequent surveillance and optimisation of MDT meetings and processes.	Conditional	Very low	Definition and consensus building to harmonise and improve MDT practices: • Preferably pan-European consensus meeting of dedicated European societies and national representatives • Creation of standardised self-assessment and/or peer-to-peer benchmark tools on MDT practices Coordinated quality improvement initiatives to optimise MDT infrastructure and processes: • Multicentric surveys and/or peer-to-peer visits for gap analyses on current MDT practices • Quality improvement studies on various aspects of MDT care, *i.e.* essential standards of documentation and case presentations as well as time management

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TABLE 2 Continued

Quality improvement measure (*versus* control)	Recommendation	Strength	Overall quality of evidence	Specific implementation considerations and research needs (international/national/regional level)
PICO 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOPs) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or SOPs?				
Guideline implementation and adherence (*versus* no guideline implementation and adherence)	*3) In patients with lung cancer, we suggest that methodologically robust, evidence-based guidelines and SOPs should be implemented and adhered to (based on informed consent by the patient).* Remark: We acknowledge that clinical practice guidelines are generally perceived as the highest level of evidence-based medicine and have been created frequently in lung cancer care. Yet, even if guidelines are issued with good methodological and contentual quality, their overall impact strongly depends on the recognition and adherence by the target audience. Stakeholder need assessments, measures to improve implementation and applicability as well as regular updates of guidelines may facilitate user acceptation. Guidelines are not mandates but do need unsolicitous approval by competent patients after provision of understandable information on recommended practices by physicians and time for discussion on their benefits and risks as well as alternatives.	Conditional	Very low	Establishing active guideline cycles in a collaborative approach: • Linkage of guideline groups (guideline development), lung cancer services (guideline implementation/adherence) and clinical lung cancer registries (quality assurance) • Frequent updates of evidence searches as well as short-handed appraisal of newly available evidence and adaption of guideline recommendations, preferably jointly among guideline groups to reduce duplication of work Monitoring and optimisation initiatives: • Acquisition of guideline adherence benchmarks: prospective multicentric observational studies among specialised lung cancer service networks assessing guideline adherence on various key recommendations and factors for non-adherence • Depiction of general care situation: retrospective/prospective population-based observational studies among clinical lung cancer registries assessing various key recommendations • Coordinated quality improvement studies on guideline implementation/adherence with mutual knowledge exchange Creation of new guideline models based on evidence from RCTs and real-world data with inclusion of artificial intelligence tools for complex diagnostic/treatment decisions and to extrapolate/adapt recommendations to patient populations not covered by RCTs

Continued

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TABLE 2 Continued

Quality improvement measure (*versus* control)	Recommendation	Strength	Overall quality of evidence	Specific implementation considerations and research needs (international/national/regional level)
PICO 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialisation for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialisation for these procedures?				
Higher hospital volume of care (*versus* lower hospital volume of care) Higher volume of care by surgeons or other professionals (*versus* lower volume of care by surgeons or other professionals)	*4) In lung cancer patients, we recommend performing lung cancer surgery a) in lung cancer services specialised in thoracic surgery with high institutional volumes of pulmonary resections and b) by surgeons specialised in thoracic surgery with high individual volumes of pulmonary resections.*	Strong (paradigmatic situation)	Very low	Quality of care research relating to better hospital and individual procedural performance quality: • Broadening of scope beyond thoracic surgical procedures • Identification of underlying causal factors • Survey-based assessment of national requirements
Better hospital specialisation (*versus* less hospital specialisation) Better specialisation of surgeons and other professionals (*versus* less specialisation of surgeons and other professionals)	*5) In lung cancer patients, we suggest performing procedures other than lung cancer surgery[#] a) in lung cancer services specialised in these procedures with high institutional volumes of these procedures and b) by professionals specialised in these procedures with high individual volumes of these procedures.* [#]: evidence available for diagnostic bronchoscopy including EBUS, quality of pathological diagnostics, different tumour-specific treatments in stage II–IV lung cancer and ICU therapy in lung cancer patients.	Conditional	Very low	• Process optimisation methods to improve or remodel operating parts within lung cancer services • Survey-based assessment of patient characteristics and preferences when re-organisation of lung cancer care is envisaged Definition and consensus building of volume of care thresholds as well as specialisation levels for hospitals and individuals: • Preferably pan-European consensus meeting of dedicated European societies and national representatives
PICO 5: In lung cancer patients (or those suspected of having lung cancer), should pathological confirmation of tumours or subtyping of lung cancers be obtained rather than no pathological confirmation of tumours or subtyping of lung cancers?				
Pathological confirmation of suspected lung cancers (*versus* no pathological confirmation of suspected lung cancers)	*6) In patients with suspected lung cancer, we recommend seeking pathological confirmation where it determines management.*	Strong (paradigmatic situation)	Very low	Quality of care research relating to pathological confirmation and subtyping of lung cancers: • Acquisition of benchmarks for pathological confirmation, histological subtyping and molecular alterations: prospective multicentric observational studies among specialised lung cancer service networks • Depiction of general care situation: retrospective/prospective population-based observational studies among clinical lung cancer registries Translational/clinical research on non-invasive or less invasive diagnostics for lung cancer confirmation and molecular subtyping: • Liquid biopsies, breath exhalate analyses, imaging techniques or combination of these
Subtyping of confirmed lung cancers (*versus* no subtyping of confirmed lung cancers)	*7) In patients with confirmed lung cancer, further subtyping of lung cancers through application of the World Health Organization (WHO) Classification of Tumours: Thoracic Tumours, 5th edition [218][#] as well as molecular characterisation for actionable targets or response to treatment should be performed.* [#]: the WHO Classification represents the internationally accepted standard.	Good practice statement		

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TABLE 2 Continued

Quality improvement measure (*versus* control)	Recommendation	Strength	Overall quality of evidence	Specific implementation considerations and research needs (international/national/regional level)
PICO 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?				
Early integration of palliative care (*versus* no early integration of palliative care)	*8) We suggest integrating palliative care already at an early stage into lung cancer care pathways based on patient symptom load and well-linked to routine tumour-specific management* Remark: Delivery of palliative care may be by palliative care specialists or palliative care teams.	Conditional	Very low	Quality of care research relating to early integration of palliative care: • Creation and assessment of graduated models to better deliver flexible needs-based palliative care alongside tumour-specific care throughout the lung cancer pathway • Survey-based assessment of patient preferences Translational/clinical research relating to early integration of palliative care: • Identification of causes and mechanisms of the assumed temporary life-prolonging effect of early palliative care integration • Definition/standardisation of core elements of early integration of palliative care • Definition/standardisation of quality assurance measures
PICO 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods?				
Application of quality improvement measures (*versus* no application of quality improvement measures)	*9) We suggest utilising national clinical lung cancer registries involving quality indicators to provide feedback for future lung cancer guidelines and to inform lung cancer services.*	Conditional	Very low	Quality improvement research in a collaborative approach: • Multicentric quality improvement studies for piloting and evaluating certain measures • Creation of open-access depositories for quality improvement measures Definition and consensus building of quality-relevant structural and processual elements as well as outcomes within lung cancer services: • Preferably pan-European consensus meeting of dedicated European societies and national representatives • Definition of an essential quality parameter catalogue for peer-to-peer visits, audits or benchmarking initiatives Set-up and prospective utilisation of high-quality multicentric lung cancer service-based registries as well as population-based registries to better facilitate future quality of care research in lung cancer (*i.e.* European Respiratory Society Clinical Research Collaboration PERSPECTIVE [16], European Union Innovative Medicines Initiative Consortium OPTIMA [17])
	10) We suggest referring lung cancer patients to services with ready access[#] to multiple lung cancer specialist facilities[¶]. [#]: ready access: reasonable proximity and timeliness; [¶]: lung cancer specialist facilities include functional diagnostics, imaging, endoscopy, pathology/molecular biology, thoracic surgery, radiotherapy, systemic treatments and palliative care, clinical trials as well as MDTs.	Conditional	Very low	
	11) We suggest developing and implementing specific quality improvement measures[+] to improve quality of lung cancer care where required and when superordinate guidance is missing [+]: *i.e.* clinical pathways.	Conditional	Very low	
	12) We suggest the implementation of an internal and/or external evaluation system[§] for lung cancer services. [§]: different terms are used beside evaluation system, *i.e.* internal/external audit system, certification system, quality indicator systems.	Conditional	Very low	

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TABLE 2 Continued

Quality improvement measure (*versus* control)	Recommendation	Strength	Overall quality of evidence	Specific implementation considerations and research needs (international/national/regional level)
PICO 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?				
Involvement of patient decision tools (*versus* no involvement of patient decision tools)	*13) In patients with lung cancer, we suggest using patient decision tools as a measure to improve patient involvement in decision making.* Remark: While current evidence does not suggest benefits from patient decision tools in lung cancer patients, we as a committee considered that the perceived positive impact on shared decision making and informed consent processes outweighs barriers for certain patient subgroups.	Conditional	Very low	Behavioural and communications research relating to patient decision tools: • Qualitative analyses on patient and professional preferences and behavioural/learning patterns • Creation and evaluation of different patient decision tool formats tailored to user preferences and capabilities Creation of patient decision tools in a collaborative approach: • Creation and evaluation of different patient decision tool formats tailored to user preferences and capabilities • Definition of essential information contents and quality standards facilitating active patient share in decision making by dedicated European/national societies and patient organisation • Creation of open-access depositories for patient decision tool contents

RCT: randomised controlled trial; EBUS: endobronchial ultrasound; ICU: intensive care unit.

contributed to this effect which were unaccounted for in the study designs (*i.e.* imminent local tumour complications with worse prognostic impact) and which may have forced clinicians to act immediately (*i.e.* salvage therapies) and by that shorten the treatment interval. Likewise, this may explain similar effects in more advanced NSCLC with higher risk for short-term tumour-related complications, both corresponding to a Will Rodgers phenomenon [86].

No further harms were identified in the 67 included studies.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency and imprecision. Applied treatment interval thresholds ranged between 7 and 90 days across studies. In addition, we considered the growing negative prognostic impact of local tumour growth as well as risk of locoregional and distant metastatic spread over time. We were aware of the substantial psychological impact on patients with suspected lung cancer and their caregivers, both warranting clinicians to ensure short waiting times from tumour detection to treatment initiation. However, we anticipate potential risks if treatment is initiated before completion of essential diagnostics that may affect management, namely access times to advanced imaging techniques and processing times of modern molecular diagnostics. Furthermore, fitness for therapy may need to be accounted for in certain patients (*i.e.* prehabilitation in comorbid patients) [87]. All are prerequisites for state-of-the-art lung cancer care. Improved overall survival through higher curative rates or at least tumour-specific treatment allocation is indeed feasible by improvement of timeliness. While local amelioration measures appear actionable with low use of resources, fundamental pathway optimisation will generate costs for healthcare systems. Yet, in the long run, a significant reduction of the large economic lung cancer burden in Europe is conceivable by coordinated measures for earlier detection and treatment [4]. In addition, there is a realistic potential for improving health equity in deprived populations or underserved regions. Thus, full acceptance by patients, medical professionals and healthcare authorities is deemed very probable.

Justifications of recommendation

Most lung cancer patients present in advanced, no longer curatively treatable stages [2]. Given the life-threatening potential of lung cancer treated too late after diagnosis, every measure on the side of primary and secondary care professionals needs to be taken to achieve timely diagnostic and treatment pathways for patients willing to be treated. Thus, we suggest minimising delay. Our recommendation is conditional due to the very low certainty of evidence and potential harms if treatment is started before completion of diagnostics or optimisation of patient fitness.

Time-points and intervals from first symptom to treatment start have been well defined in the Aarhus statement paper [88]. A recent review summarised varying arbitrary national timeliness requirements, none of which were evidence based or internationally consented [18]. At this stage, we have therefore deliberately refrained from naming specific requirements from an international perspective.

Conclusions, implementation considerations and research needs

Despite lack of evidence on many of our predefined outcomes, we are confident that optimising waiting times is an important measure to improve outcomes in lung cancer care. With the implementation of population-based lung cancer screening programmes on the horizon, at-risk individuals will benefit from effective information campaigns encouraging them to seek prompt medical attention when experiencing alarm symptoms. In contrast, treatment intervals in modern systemic therapies based on molecular lung cancer profiling have still not yet been systematically explored.

PICO Question 2: In patients with lung cancer (or those suspected of having lung cancer), should a multidisciplinary team (MDT) or certain disciplines be involved rather than no involvement of an MDT or certain disciplines?

ERS recommendation

2) *We suggest the integration of MDTs and/or multidisciplinary consultation in the management of patients with (suspected) lung cancer.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

Remark: We acknowledge that MDTs are already implemented broadly in lung cancer care, yet to achieve good integration, we see the need for better implementation of multidisciplinary teamwork throughout the lung cancer pathway as well as for frequent surveillance and optimisation of MDT meetings and processes.

Problem

Multidisciplinary approaches facilitate interprofessional collaboration leading to joint discussion and consensus on personalised diagnostic and therapeutic strategies for patients, yet also provide challenges to lung cancer services [89]. Thus, we considered it important to systematically assess the benefits and potential downsides of lung cancer MDTs.

Summary of evidence and overall quality of evidence

We identified 25 observational studies and one RCT out of the 874 initial abstracts [19, 76, 90–113]. To enable clinically meaningful pooling of data, we formed four subgroups: 1) all lung cancer, all stages, all treatment modalities; 2) NSCLC, all stages, all treatment modalities; 3) NSCLC, all stages, surgical resection; and 4) NSCLC, stage III/IV, all treatment modalities. From our predefined outcomes of interest, the following were reported in the included studies: *overall survival*, *30-day mortality*, *morbidity*, *accuracy of staging*, *pathological confirmation*, *receipt of curative treatment*, *receipt of any tumour-specific treatment*, *quality of life* and *patient satisfaction*. All outcomes were considered either critical or important. The overall quality of evidence was rated as very low.

Desirable effects

Benefits of implementing MDT measures differed among the predefined subgroups. However, MDT measures resulted in improved overall survival according to the meta-analyses in NSCLC in stage III/IV (HR 0.750, 95% CI 0.623–0.903) and in all stages (all treatments: HR 0.759, 95% CI 0.614–0.939; surgical resection: HR 0.765, 95% CI 0.496–1.145) as well as cohorts incorporating all lung cancer types (HR 0.618, 95% CI 0.578–0.662), lower 30-day mortality in resected NSCLC, better accuracy of staging in the subgroup analyses for early and advanced NSCLC, higher pathological confirmation rates for all lung cancer types and resected NSCLC, higher rates of receipt of curative treatment in subgroup assessments of all lung cancer types and resected NSCLC, and higher rates of receipt of any tumour-specific treatment in all four subgroups.

Undesirable effects

No clinically meaningful harms were seen resulting from MDT interventions.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency and imprecision. The limited evidence basis may be partially explained since MDT meetings have been commonly established for many years worldwide in routine cancer care impeding related quality of care research due to lack of patients treated outside from multidisciplinary structures. We see major benefits in MDTs including interprofessional collaboration and consensus finding on personalised management strategies. For us, resulting desirable effects are reduction in clinical practice variability, shortened and standardised decision processes balancing patient preferences and guideline-recommended care.

At the same time, patients value and benefit from multidisciplinary teamwork, which has already become an obligation by health authorities in many countries. Despite the progress already made, multidisciplinary consultation and set-up of corresponding elements of care still need to be broadened across the lung cancer continuum. We see potential needs for improvement of MDT meetings and processes based upon periodic monitoring. Implementation seems feasible to us as the provision of needed resources may be compensated by saved expenditures for avoided under-, over- and mistreatment.

Justifications of recommendation

Multidisciplinary structures and processes seem necessary to ensure the best personalised diagnostic and therapeutic strategies for patients. There were no evident substantial harms related to implementation of MDT measures. Thus, we suggest the implementation of MDT measures, even if the survival benefit is not always clear. The recommendation is conditional due to the very low certainty of evidence which is additionally limited to few of our predefined outcomes.

Conclusions, implementation considerations and research needs

Multidisciplinary care represents a holistic approach to ensure good clinical and patient-centred lung cancer care. It has become medico-legally mandatory in various countries. Comprehensive essential and advanced MDT standards were first issued by an ERS Task Force in 2018 [7], which were later further developed by another European initiative in 2020 [114]. Yet, in practice, MDTs need to be committed to broaden their actions throughout the lung cancer continuum and optimise them based on self-assessment at regular intervals [115].

PICO Question 3: In patients with lung cancer (or those suspected of having lung cancer), should guidelines or standard operating procedures (SOPs) for lung cancer care be implemented or adhered to rather than non-implementation of or non-adherence to these guidelines or SOPs?

ERS recommendation

3) In patients with lung cancer, we suggest that methodologically robust, evidence-based guidelines and SOPs should be implemented and adhered to (based on informed consent by the patient). (Conditional recommendation for the intervention; very low overall quality of evidence.)

Remark: We acknowledge that clinical practice guidelines are generally perceived as the highest level of evidence-based medicine and have been created frequently in lung cancer care. Yet, even if guidelines are issued with good methodological and contentual quality, their overall impact strongly depends on the recognition and adherence by the target audience. Stakeholder need assessments, measures to improve implementation and applicability as well as regular updates of guidelines may facilitate user acceptance. Guidelines are not mandates but do need unsolicitous approval by competent patients after provision of understandable information on recommended practices by physicians and time for discussion on their benefits and risks as well as alternatives.

Problem

Large numbers of international and national lung cancer guidelines exist with significantly varying methodological quality and partially outdated recommendations. Higher national financial resources correlated with enhanced guideline quality [6, 116]. Dissemination, implementation, adherence and updates are the essential next steps within the guideline cycle introduced by the European Commission in 2004, ensuring value-added utilisation of well-developed guidelines [117]. Yet, in real-life, difficulties in guideline implementation and adherence among professionals [118, 119] and stakeholders [120, 121] were identified, while some evidence indicated limited impact and substantial variation of assisting tools for guideline implementation [122].

Summary of evidence and overall quality of evidence

15 observational studies were finally selected out of the 754 initially identified abstracts [123–137]. To allow clinically meaningful rating of evidence, we defined six subgroups: *guideline implementation*: 1) all lung cancer, all stages, all therapies; *guideline adherence*: 2) NSCLC, all stages, surgical resection with or without neoadjuvant/adjuvant therapies; 3) all lung cancer, all stages, all treatment modalities; 4) NSCLC, unresectable stage III, chemo- and/or radiotherapy; 5) NSCLC, all stages, chemotherapy; and 6) SCLC, all stages, all treatment modalities. The included studies addressed the following outcomes that were *a priori* assessed as important or critical: *overall survival*, *30-day mortality*, *morbidity*, *accuracy of staging*, *receipt of curative treatment* and *receipt of any tumour-specific treatment*. The overall quality of evidence was rated as very low.

Desirable effects

Improved overall survival, post-surgical 30-day mortality, accuracy of staging, receipt of curative treatment and receipt of any tumour-specific treatment were seen in the Danish national guideline implementation initiative linked to the re-organisation of lung cancer services and the set-up of a national clinical lung cancer registry [128, 129], whereas a comparable earlier study from the UK showed positive effects on overall survival relating to some organisational standards [130].

Guideline adherence to single or combined recommendation-derived quality measures improved overall survival in the context of NSCLC thoracic surgery [134–136], chemo-/radiotherapy in stage III NSCLC [123] and various SCLC treatment modalities [127].

Undesirable effects

None of the evaluated studies indicated any substantial harms regarding guideline implementation or adherence. The calculated opposite negative effect on overall survival in the work by Odell *et al.* [134] suggesting non-adherence to the evidence-based recommendation to initiate neo-adjuvant therapy before surgery in clinical stage IIIA NSCLC patients was invalidated by the authors due to a disproportionate, potentially non-representative control arm.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency and imprecision. Meta-analyses were not meaningful in any of the predefined groups. Nevertheless, we value methodologically robust guidelines (currently best measured by the AGREE II tool [138]) as the most valid sources in evidence-based medicine facilitating good standardised care.

We see certain risks deriving from outdated guideline recommendations and the surplus of available guidelines on certain topics with sometimes contradicting recommendations. In addition, we note that guideline recommendations cannot be transferred into patient management in all cases due to potential contraindications, but also note opportunities for individualised treatment concepts. Funding of guidelines by healthcare authorities or industry may be accompanied by certain limitations, namely the constraints to nationally available resources or less transparent, objective conclusions, respectively [139].

Ensuring equity among patients receiving guideline-concordant care should be an unquestionable goal. Based on Surveillance, Epidemiology, and End Results Medicare (SEER) US data, Fang *et al.* [140] detected that Black race patients compared to White race patients were less likely to receive stereotactic radiation or surgery in stage I NSCLC (14 605 patients; 61% *versus* 75%; p<0.0001) as well as chemotherapy in addition to radiotherapy or surgery in stage III NSCLC (15 609 patients; 36% *versus* 41%; p<0.0001).

No increased costs after guideline implementation were detected by Casebeer *et al.* [126] after multivariate analysis. Neubauer *et al.* [132] could even demonstrate lower costs for guideline-concordant care within a period of 1 year after initiation of first-line chemotherapy in NSCLC patients in a regional outpatient US oncology network (1409 patients; average 12-month on/off pathway costs: USD 18 042 *versus* USD 27 737; on/off cost ratio 0.71, 95% CI 0.64–0.80).

Justifications of recommendation

While there is very low level of certainty in the effect estimates, we recognise the aforementioned benefits of guidelines and the limited potential for harms when evidence-based recommendations are properly implemented and used to inform practice (*e.g.* supporting appropriate clinical decision making with the patient).

Conclusions, implementation considerations and research needs

The aforementioned potential problems of creation, dissemination and implementation as well as maintaining up-to-date guidelines should be considered and actively addressed in respective national, regional and local settings. Systematic surveillance of guideline implementation and adherence is desirable, but currently often fails due to insufficient data sources as well as width, quality and completeness of data. Valuable financial and human resources for guideline development may be saved by multidisciplinary collaborations across societies and governmental bodies within and between countries as well as on the international level, avoiding unnecessary duplication of work within the evidence synthesis. However, evidence-based guideline recommendations are usually adapted according to different national healthcare system organisation and resources (among many others, a positive example is the conjoint development and implementation of the Belgian Lung Cancer Guideline led by the Belgian Health Care Knowledge Centre KCE [141]).

PICO Question 4: Should patients with lung cancer (or those suspected of having lung cancer) receive lung cancer-specific diagnostic or therapeutic procedures in hospitals/from professionals with higher volumes of activity/with a higher grade of specialisation for these procedures rather than receiving them in hospitals/from professionals with lower volumes of activity/with lower grade of specialisation for these procedures?

ERS recommendation

4) *In lung cancer patients, we recommend performing lung cancer surgery a) in lung cancer services specialised in thoracic surgery with high institutional volumes of pulmonary resections and b) by surgeons specialised in thoracic surgery with high individual volumes of pulmonary resections.* (Strong recommendation for the intervention; paradigmatic situation in very low overall quality of evidence.)

5) *In lung cancer patients, we suggest performing procedures other than lung cancer surgery[#] a) in lung cancer services specialised in these procedures with high institutional volumes of these procedures and b) by professionals specialised in these procedures with high individual volumes of these procedures.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

[#]: evidence available for diagnostic bronchoscopy including endobronchial ultrasound (EBUS), quality of pathological diagnostics, different tumour-specific treatments in stage II–IV lung cancer and intensive care unit (ICU) therapy in lung cancer patients.

Problem

Over the last three decades, numerous studies reported that higher procedural volumes or better specialisation of care delivered by hospitals and clinicians lead to improved outcomes in lung cancer patients. However, the knowledge of this positive correlation has still not yet been fully translated into routine care [142].

Summary of evidence and overall quality of evidence

76 observational studies were finally selected out of the 440 initially identified abstracts [85, 103, 143–216]. To allow clinically meaningful rating of evidence, we defined six subgroups: 1) all lung cancer, all stages, hospital volume of surgical resections; 2) all lung cancer, all stages, hospital specialisation in surgical resections; 3) all lung cancer, all stages, surgeon volume of surgical resections; 4) all lung cancer, all stages, surgeon specialisation in surgical resections; 5a–i) hospital volume of procedures other than surgical resection; and 6a and b) hospital specialisation in procedures other than surgical resection. The included studies addressed the following outcomes that were *a priori* assessed as important or critical: *overall survival*, *progression-free survival*, *mortality*, *morbidity*, *accuracy of staging*, *pathological confirmation* and *receipt of curative treatment*. The overall quality of evidence was rated as very low.

Desirable effects

Regarding surgical resections, the following desirable effects were seen: improved overall survival, reduced mortality rates (studies applied in-hospital, 30-day, 60-day or 90-day mortality) and reduced rates of certain types of morbidity in 1) hospitals with higher volumes, 2) better specialised hospitals, 3) surgeons with higher individual volumes and 4) better specialised surgeons. More accurate staging was detected in better specialised hospitals and surgeons; likewise, higher surgical resection rates were detected in these two subgroups as well as in hospitals with higher volumes.

Due to substantial heterogeneity in terms of patient populations, extent of pulmonary resections as well as number and thresholds of volume strata or categorisation of specialisation across studies resulting in very low or low certainty in the evidence, we did not conduct any meta-analyses in all four subgroups. Nevertheless, based on our self-selected evaluation scheme to estimate the effect sizes of single studies, for all addressed outcomes in the four subgroups, the number and pooled patient data of studies with large effects outnumbered those of studies with trivial effects when comparing highest *versus* lower volumes or best *versus* least defined grade of specialisation. Additionally, we detected several studies with moderate and small effects (see PICO 4 evidence tables, subgroups 1–4 in supplementary material B for detailed effect sizes).

The evidence basis on procedures other than surgical resections (subgroup 5a–i) was limited and focused on hospital volumes and specialisation only. Here we detected in 5a) *diagnostic bronchoscopies including EBUS* improved 7-day, 15-day and 30-day mortality rates in hospitals with higher volumes (one study, large effect, 77 755 patients), 5b) *quality of pathological lung cancer diagnostics* more accurate pathological diagnoses in hospitals with higher volumes and better specialised hospitals (both in one study, large effect, 89 409 lung cancer specimens), 5c) *chemoradiotherapy in stage II/IIIA NSCLC* improved overall survival (two studies large effects, 734 patients) and progression-free survival (one study, moderate effects, 495 patients) in hospitals with higher volumes, 5d) *different treatment modalities in stage IIIA NSCLC* improved overall survival and receipt of curative treatment in hospitals with higher volumes (both in one study, large effects, 83 673 patients, 5e) *systemic therapies in stage III/IV lung cancer* likely improved 30-day mortality in hospitals with higher volumes (one study, trivial effect, 26 277 patients)), 5f) *different treatment modalities in stage IV NSCLC* improved overall survival and receipt of curative treatment in hospitals with higher volumes (both in one study, large effects, 338 445 patients), 5g) *different treatment modalities in all-stage NSCLC* improved receipt of curative treatment in hospitals with higher volumes and better specialised hospitals (both in one study, large effects, 43 544 patients), 5h) *different treatment modalities in all-stage lung cancers* improved overall survival in hospitals with higher volumes (one study, large effect, 9235 patients), and 5i) *ICU therapy in lung cancer patients* improved 30-day and 180-day mortality rates in hospitals with higher volumes (both in one study, large effects, 499 patients).

Undesirable effects

None of the evaluated studies indicated any substantial harms regarding higher volumes of care or better specialisation.

Other considerations

The implementation of medico-legal requirements concerning volumes and specialisation of hospitals and surgeons related to lung cancer surgery and the potential consequence of the need for re-organisation of lung cancer services seems feasible on national levels across Europe and has already taken place. The Danish healthcare system successfully pursued this implementation through reduction and subsequent regional centralisation of thoracic surgery services with adjacent satellite centres for local diagnostics and systemic therapies, all in close collaboration with lung cancer-related societies and professionals [217].

Regionalisation of care to achieve higher volumes and better specialisation may reduce proximity to suitable lung cancer services and by that impose burden on some patients.

Justifications of recommendations

We have acknowledged that differing individual, institutional and healthcare system factors as well as patient preferences could not be fully accounted for in the retrospective observational studies and few RCTs. Yet, regarding lung cancer surgery, the body of evidence contained a considerable number of studies from different countries and many with large patient numbers or even population-based observational designs. Most studies justified the recommendation; none showed a converse correlation. Despite the varying level of confidence from moderate to low and very low in the respective effect estimates for hospital as well as surgeon volume and specialisation, a strong recommendation for the aforementioned lung cancer surgery performance is warranted given the life-threatening potential of lung cancer, especially when operated improperly (very low quality of evidence suggesting benefit in a life-threatening situation as a paradigmatic scenario in accordance with GRADE methodology) [15]. No substantial harms were evident or foreseen by us. Patient preferences need to be addressed and acknowledged in joint decision making.

Given the limited body of evidence for the other named diagnostic and therapeutic procedures, only conditional recommendations were consented.

Purposely, no lower thresholds narrowing the best volume of activity were defined at this stage for any of the appraised procedures since these would need additional consensus by relevant stakeholders on the national level. Thresholds for institutional and surgeon high volumes utilised in the analysed studies ranged from 10 to 468 and six to 132 surgical resections per year, respectively. Likewise, no upper thresholds were defined by us despite bearing in mind that resources are limited and that excessive volumes of care may lead to potentially harmful resource depletion within all procedures.

Conclusions, implementation considerations and research needs

Further patient-centred quality of care research is needed to better identify and describe underlying factors leading to better quality of hospitals and individual professionals as well as to define lower and upper thresholds for volumes of care in lung cancer-related procedures.

PICO Question 5: In lung cancer patients (or those suspected of having lung cancer), should pathological confirmation of tumours or subtyping of lung cancers be obtained rather than no pathological confirmation of tumours or subtyping of lung cancers?

ERS recommendation

6) *In patients with suspected lung cancer, we recommend seeking pathological confirmation where it determines management.* (Strong recommendation for the intervention; paradigmatic situation in very low overall quality of evidence.)

7) *In patients with confirmed lung cancer, further subtyping of lung cancers through application of the World Health Organization (WHO) Classification of Tumours: Thoracic Tumours, 5th edition [218]# as well as molecular characterisation for actionable targets or response to treatment should be performed.* (Good practice statement.)

#: the WHO Classification represents the internationally accepted standard.

Problem

Due to the considerable expansion of therapeutic options over the last decade, diligent tumour biological profiling of lung cancers is considered as an essential prerequisite to tailor personalised treatments. However, its availability seems very heterogeneous within and across countries [6].

Summary of evidence and overall quality of evidence

Seven observational studies were finally selected out of the 759 initially identified abstracts which reported on *overall survival*, *progression-free survival* and *receipt of any tumour-specific treatment* [219–225]. All outcomes were considered critical. All studies related to pathological confirmation of lesions suspicious for lung cancer. To allow for clinically meaningful rating of evidence, we formed two subgroups: 1) all lung cancer types, all stages, all treatment modalities; and 2) NSCLC, stage I/II, stereotactic radiotherapy. No evidence was retrieved for histological subtyping as well as molecular characterisation of confirmed lung cancers directly applicable to this search question. The overall quality assessment of evidence was rated as very low.

Desirable effects

Regarding pathological confirmation, large effects with improved overall survival were seen in two studies with unselected patients for all lung cancers (511 patients) and NSCLC (5906 patients), respectively. Likewise, the largest study demonstrated enhanced overall survival in the defined subgroups, yet the effect strength decreased with higher age and poorer performance status (136 993 patients). In one study, pathological confirmation in NSCLC patients had a large effect on higher rates of tumour-specific treatments (5906 patients).

Undesirable effects

The subgroup analysis by Khakwani *et al.* [221] indicated that elderly patients as well as those with poor performance status did not benefit from pathological confirmation of suspicious lesions, which may be due to lack of therapeutical benefit as well as higher diagnostic procedural risk and/or reduced fitness for subsequent therapy.

Only trivial effects were seen, suggesting lower overall and progression-free survival in the clinically suspected stage I/II patients receiving stereotactic radiotherapy without prior pathological confirmation. Yet, a bias seemed likely here due to the unavoidable inclusion of individuals with non-malignant solitary pulmonary nodules (with better prognosis) in the cohort with no pathological confirmation.

Otherwise, none of the evaluated studies of both subgroups indicated any substantial peri-procedural harms resulting from pathological confirmation.

Other considerations

The direct evidence with reference to pathological confirmation was very limited and graded as very low due to concerns about risk of bias, indirectness and imprecision. However, the panel felt that a substantial body of indirect evidence demonstrated the added value of pathological confirmation as a prerequisite for more effective and less harmful personalised treatment decisions. While no direct evidence was retrieved with reference to histological subtyping and molecular profiling of lung cancers compared to their non-execution, both are generally accepted mainstays for personalised therapy planning in lung cancer following several therapeutic RCTs [226]. Additionally, the approval of several systemic drugs by the European Medicines Agency is based on this indirect, high-level evidence, most often with the mandatory prerequisite to determine the respective molecular targets or predictive markers before prescription of any of these drugs [227]. The panel acknowledged the need to avoid performing invasive diagnostics in unfit patients.

Justifications of recommendations

Improvements in pathological confirmation rates and thorough profiling of lung cancers by light microscopy, immunohistochemistry and molecular techniques have been one of the major advances in lung cancer care with substantial predictive and prognostic impact [226]. While the limited direct evidence basis of very low overall quality suggests equivalence of pathological confirmation *versus* non-confirmation, the aforementioned indirect evidence of high quality showed less harm in treating patients with pathologically confirmed lung cancers as tumour material is the fundamental requirement for subsequent tumour profiling. Thus, we consented a strong recommendation for pathological confirmation of suspected lung cancer since this constellation constitutes a paradigmatic situation according to GRADE methodology [15].

To underline the need and net benefit of performing histological subtyping and molecular profiling in confirmed lung cancers, we formulated a clear and actionable good practice statement given that direct evidence was missing as well as to avoid time-consuming efforts to formally accumulate and review the already well-established and supportive indirect evidence of high quality [228].

Conclusions, implementation considerations and research needs

While pathological confirmation (whenever feasible), WHO lung cancer classification-compliant subtyping and characterisation of treatable or predictive molecular targets are deemed as good clinical practice, valid evidence on their implementation in routine lung cancer diagnostics is still lacking for the most part. Substantial advances in imaging validity as well as endoscopic procedures, transthoracic computed tomography/ultrasound-guided, minimally invasive thoracic surgery and the multidisciplinary interplay of professionals have led to a reduction of peri-procedural risks of invasive sampling techniques.

PICO Question 6: In patients with lung cancer (or those suspected of having lung cancer), should palliative care or its delivery by specialists be integrated into lung cancer care already early during the course of the disease rather than no integration of palliative care or no palliative care delivery by specialists?

ERS recommendation

8) We suggest integrating palliative care already at an early stage into lung cancer care pathways based on patient symptom load and well-linked to routine tumour-specific management. (Conditional recommendation for the intervention; very low overall quality of evidence.)

Remark: Delivery of palliative care may be by palliative care specialists or palliative care teams.

Problem

There is a growing body of evidence for early integration of palliative care into standard care in lung cancer as well as in other tumour entities which may positively influence quality of life, patient satisfaction and prognosis. However, this potentially beneficial practice is still not regularly implemented into routine processes [229].

Summary of evidence and overall quality of evidence

We included 23 RCTs, two non-RCTs with a prospective sequential control–intervention group design and five observational studies out of the 269 primarily identified abstracts [230–259]. Out of the predefined outcomes of interest, *overall survival*, *receipt of any tumour-specific therapy*, *quality of life* and *patient satisfaction* were explored in the 30 studies. All outcomes were considered critical. The overall quality of evidence was rated as very low.

Desirable effects

Improved overall survival was seen in the meta-analysis of one RCT and one non-RCT providing lung cancer-specific findings for patients receiving palliative care alongside standard care (HR 1.383, 95% CI 1.047–1.824). The receipt of any tumour-specific treatment was not influenced by early integration in one RCT. Quality of life improved in four (509 patients) compared to 18 RCTs with trivial effects (1238 patients). Four studies revealed only trivial effects regarding patient satisfaction (at least 101 lung cancer patients; no lung cancer-specific data in three studies). The heterogeneity of quality of life and patient satisfaction tools across studies impeded meta-analyses.

Undesirable effects

None of the evaluated studies indicated any definite harms by early integration of palliative care.

Other considerations

We determined very low certainty due to concerns about risk of bias, indirectness, inconsistency and imprecision. Standards for palliative care were previously defined by the European Association for Palliative Care in 2009/2010 [260, 261] and similarly for the USA by the National Consensus Project for Quality Palliative Care in 2013 [262]. Yet, the modes of palliative care differed substantially in the appraised studies related to composition of palliative care teams as well as to content and extent of applied palliative care measures. Although not evident, in our perception, integrating palliative care early into standard lung cancer care has improved over time, but there still seems to be coexistence instead of joint patient care, bearing the risk of contradictory treatment recommendations to patients by lung cancer and palliative care specialists. Likewise, we may not ignore the need to overcome the still existing stigma of palliative care as a “terminal care only” measure to reduce prevalent reservations among patients and professionals.

At least a moderate increase of costs is assumed by us regarding comprehensive programmes for implementation of palliative care into standard lung cancer care, yet sufficient cost-effectiveness models have not been introduced so far.

Justifications of recommendation

Due to the high symptom burden in lung cancer patients, we consider early integration of palliative care into standard lung cancer care as an effective measure to address the complex patient needs already at the beginning of the lung cancer continuum. The recommendation is conditional due to the very low certainty of evidence.

Conclusions, implementation considerations and research needs

The implementation of palliative care elements seems feasible when sufficient funding is provided. Joint strategies by governments and scientific societies are favoured, including standardisation of palliative care measures and related quality indicators to assess outcomes. Professionals not specialised in palliative care would benefit from respective training to support coping with unmet needs [229].

PICO Question 7: In patients with lung cancer (or those suspected of having lung cancer), should quality improvement measures be applied in lung cancer care rather than no application of these methods?

ERS recommendations

9) *We suggest utilising national clinical lung cancer registries involving quality indicators to provide feedback for future lung cancer guidelines and to inform lung cancer services.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

10) *We suggest referring lung cancer patients to services with ready access[#] to multiple lung cancer specialist facilities[¶]*. (Conditional recommendation for the intervention; very low overall quality of evidence.)

    [#]: ready access: reasonable proximity and timeliness; [¶]: lung cancer specialist facilities include functional diagnostics, imaging, endoscopy, pathology/molecular biology, thoracic surgery, radiotherapy, systemic treatments and palliative care as well as MDTs.

11) *We suggest developing and implementing specific quality improvement measures[+] to improve quality of lung cancer care where required and when superordinate guidance is missing.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

    [+]: *i.e.* clinical pathways.

12) *We suggest the implementation of an internal and/or external evaluation system[§] for lung cancer services.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

    [§]: different terms are used beside evaluation system, *i.e.* internal/external audit system, certification system, quality indicator systems.

Problem

Quality improvement measures for lung cancer care aim to improve infrastructure, processes and patient outcomes at the same time, although their specific impact has rarely been systematically assessed.

Summary of evidence and overall quality of evidence

We selected 13 observational studies out of the 1037 initially identified abstracts [128, 217, 263–273]. To allow clinically meaningful assessments and separate recommendations, we formed four subgroups: 1) cancer registries and quality indicators; 2) specialised lung cancer services; 3) quality improvement measures; and 4) audits/quality indicator systems. From the predefined outcomes of interest, *overall survival*, *mortality*, *accuracy of staging*, *pathological confirmation*, *receipt of curative treatment* and *receipt of any tumour-specific treatment* were addressed in these study groups. All outcomes were considered critical. The overall quality of evidence was rated as very low.

Desirable effects

The implementation of cancer registries and quality indicators resulted in improvement of overall survival, mortality, accuracy of staging, pathological confirmation, receipt of curative therapy and receipt of any tumour-specific treatment. While exploring the impact of specialised lung cancer services, three studies demonstrated improved overall survival compared to less specialised lung cancer services. Likewise, one study also proved higher rates of receipt of any tumour-specific treatment.

Specific quality improvement measures positively affected overall survival, accuracy of staging and receipt of any tumour-specific treatment.

Three studies demonstrated better 30-day mortality resulting from the application of audits/quality indicator systems. One study additionally detected lower morbidity rates.

Undesirable effects

We did not identify any harms in the four predefined subgroups.

Other considerations

The very low certainty resulted from noted risk of bias, indirectness, inconsistency and imprecision. We considered higher satisfaction of patients and staff as an additional benefit, but were concerned about the lack of standardisation and validation.

Quality improvement measures may be resource intensive and impose costs to local healthcare providers as well as national healthcare systems which may be outweighed by avoided costs for non-conformity to lung cancer care standards.

Justifications of recommendations

We are confident that all four types of quality improvement measures bear the potential to optimise lung cancer processes and to improve patient-relevant outcomes. The limited and heterogeneous body of evidence with a very low level of confidence in the effect estimates led to conditional recommendations.

Conclusions, implementation considerations and research needs

Quality improvement initiatives based on the explored measures seem essential for achieving and maintaining an adequate, state-of-the-art management of lung cancer patients. Yet, these measures need to be adapted according to future research and evidence-based developments.

PICO Question 8: In patients with lung cancer (or those suspected of having lung cancer), should patient decision tools be involved in the decision-making and -sharing process rather than not involving them?

ERS recommendation

13) *In patients with lung cancer, we suggest using patient decision tools as a measure to improve patient involvement in decision making.* (Conditional recommendation for the intervention; very low overall quality of evidence.)

Remark: While current evidence does not suggest benefits from patient decision tools in lung cancer patients, we as a committee considered that the perceived positive impact on shared decision making and informed consent processes outweighs barriers for certain patient subgroups.

Problem

Provision of patient information and obtainment of patient consent are fundamental ethical and legal requirements within the medical profession. However, the knowledge gap in the physician–patient relationship may impose a barrier in communication and decision making.

Summary of evidence and overall quality of evidence

The initially phrased PICO question focused on patient involvement as a whole. Yet, due to the scarce body of evidence retrieved by the corresponding literature search, we could only focus on patient decision tools as an intervention to facilitate better patient involvement in the shared decision-making process. Accordingly, we narrowed the scope of the original PICO question. Five RCTs were finally selected out of the 357 initially identified abstracts [274–278]. From the predefined outcomes of interest, the identified studies assessed solely *patient satisfaction.* This outcome was considered critical. The overall quality of evidence was rated as very low.

Desirable effects

Patient satisfaction was the sole outcome of interest reported in all five RCTs. None reported lung cancer-specific results. One study resulted in improved patient satisfaction when applying patient decision tools (629 patients) [278], while four studies had trivial findings (726 patients) [274–277].

Undesirable effects

None of the evaluated studies indicated any definite harms.

Other considerations

We concluded a very low certainty in the limited evidence due to concerns about risk of bias, indirectness, inconsistency and imprecision. From our point of view, patient decision tools may additionally facilitate better disease understanding and more structured patient–professional communication. Consequently, shared decision making, informed consent processes and patient satisfaction may result. We regard factors such as age, language barriers, educational and cultural background as well as the readiness to receive and recognise bad news as potential limitations.

Justifications of recommendation

Patient decision tools, if well designed and implemented, may improve patient satisfaction and facilitate disease understanding. However, as our graded certainty in the limited body of evidence was very low level and only one of our outcomes of interest was addressed, we made a conditional recommendation.

Conclusions, implementation considerations and research needs

Needs assessments among lung cancer patients and patient organisations as well as setting up essential standards may help to develop better patient-tailored decision tools at a sufficient quality level. In addition, modern learning theory approaches should be considered.

Summary

Based on a thorough systematic literature search, this ERS Task Force compiled a comprehensive evidence basis relating to eight relevant PICO questions in quality of lung cancer care. In accordance with GRADE methodology, in several instances the systematic review revealed only sparse available evidence and for all eight PICO questions only a very low overall quality of evidence. While the certainty of effect directions suggested that implementation of quality improvement measures resulted in at least some ameliorations in 107 of all 112 assessed outcomes in the eight PICO questions, the interpretation of effect strengths was sometimes difficult due to inconsistency and imprecision among studies. Likewise, the body of evidence did not address several outcomes of interest in some PICO questions. Nevertheless, after careful considerations among our multidisciplinary Task Force panel including patient representatives, we are convinced that the deliberate implementation of our recommendations can sustainably improve quality and outcomes of lung cancer patient care. In addition, we are confident that this work will set a basis for future quality of care research and specific qualitative improvement initiatives in patient-centred lung cancer care.

Two strong recommendations were made regarding volume and specialisation of care related to hospitals and individuals in surgical resections as well as pathological confirmation of suspected lung cancers. The panel felt that strong recommendations were warranted based on eligible paradigmatic scenarios with very low quality of evidence suggesting benefit in a life-threatening situation as well as very low quality of evidence suggesting equivalence of both alternatives but high quality of evidence of less harm in the intervention, respectively [15].

10 conditional recommendations were made regarding timeliness of care, implementation of MDTs and/or multidisciplinary consultation, guideline and SOP implementation/adherence, volume and specialisation of care in procedures other than surgical resections, early integration of palliative care, implementation of quality improvement measures, and the application of patient decision tools in patient decision making.

Finally, one good practice statement was formulated on subtyping of confirmed lung cancers justified by the predefined GRADE criteria [228].

The present recommendations should be reconsidered as new evidence becomes available.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health

professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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