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Original research

Association between time-to-treatment and outcomes in non-small cell lung cancer: a systematic review

Helen Hall [1], Adam Tocock,[2] Sarah Burdett [3], David Fisher,[3] William M Ricketts [4], John Robson,[5] Thomas Round,[6] Sarita Gorolay,[7] Emma MacArthur,[8] Donna Chung,[8] Sam M Janes [1], Michael D Peake,[8,9] Neal Navani [1,10]

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For numbered affiliations see end of article.

Correspondence to
Dr Neal Navani, UCL Respiratory, University College London, 5 University Street, London, WC1E 6JF, UK; n.navani@ucl.ac.uk

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ABSTRACT

Background National targets for timely diagnosis and management of a potential cancer are driven in part by the perceived risk of disease progression during avoidable delays. However, it is unclear to what extent time-to-treatment impacts prognosis for patients with non-small cell lung cancer, with previous reviews reporting mixed or apparently paradoxical associations. This systematic review focuses on potential confounders in order to identify particular patient groups which may benefit most from timely delivery of care.

Methods Medline, EMBASE and Cochrane databases were searched for publications between January 2012 and October 2020, correlating timeliness in secondary care pathways to patient outcomes. The protocol is registered with PROSPERO (the International Prospective Register of Systematic Reviews; ID 99239). Prespecified factors (demographics, performance status, histology, stage and treatment) are examined through narrative synthesis.

Results Thirty-seven articles were included. All but two were observational. Timely care was generally associated with a worse prognosis in those with advanced stage disease (6/8 studies) but with better outcomes for patients with early-stage disease treated surgically (9/12 studies). In one study, patients with squamous cell carcinoma referred for stereotactic ablative radiotherapy benefited more from timely care, compared with patients with adenocarcinoma. One randomised controlled trial supported timeliness as being advantageous in those with stage I–IIIA disease.

Conclusion There are limitations to the available evidence, but observed trends suggest timeliness to be of particular importance in surgical candidates. In more advanced disease, survival trends are likely outweighed by symptom burden, performance status or clinical urgency dictating timeliness of treatment.

Key messages

What is the key question?

⇒ To what extent does the timeliness of secondary care pathways impact outcomes in patients with non-small cell lung cancer.

What is the bottom line?

⇒ Shorter times to treatment appear to be of greatest importance in those undergoing surgery treatment with curative intent, but do not appear to confer an advantage in patients with advanced disease.

Why read on?

⇒ Our review is the first to address the evidence base for timeliness with a priori consideration for factors including demographics, histology, stage and treatment, and identifies patient groups at highest risk of adverse outcomes as a consequence of delays to treatment.

INTRODUCTION

Lung cancer remains the most common cause of cancer-related death worldwide,[1] largely due to the majority of patients being diagnosed with advanced stage disease, precluding treatment with curative intent.[2] Instigating treatment as early as possible can maximise the benefits from curative intervention[3] and, where advanced disease is already present, help initiate systemic therapies before clinical decline.[4] In striving for this, primary care awareness and early referral,[5] low-dose CT (LDCT) screening for high-risk groups[6 7] and timeliness of secondary care pathways all require consideration.

Targets for timely investigation and management are driven in part by the risk of disease progression during avoidable delays. However, non-small cell lung cancer (NSCLC) displays both clinical and biological heterogeneity[8] and some patients may benefit disproportionately from expedient care. Four previous reviews[9–12] have explored the prognostic impact of timeliness in secondary care on patients with NSCLC. All report common limitations with heterogeneous evidence precluding quantitative analyses, and overall conclusions describe contradictory or paradoxical results with timeliness often associated with worse outcomes.[9–12] A common emerging theme is the so-called 'waiting-time paradox',[12] whereby more unwell patients with advanced disease receive more expedient treatment, thus suggesting a protective effect from treatment delays.[12 13] Disentangling this requires consideration of factors likely to impact both

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Table 1 PICOS question and inclusion/exclusion criteria

	Inclusion	Exclusion
Patient	► Any patient aged ≥18 years ► Diagnosed with NSCLC ► Investigations and treatment performed in an elective secondary or tertiary care setting	► NSCLC not examined in isolation from other cancer diagnoses ► Non-standard or emergency care pathways included ► Time intervals not measurable or not relevant to secondary/tertiary care
Intervention	► Any with the intention of reducing part or all of time intervals from primary care referral to treatment	NA
Control	► Usual care	NA
Outcome	► Lung cancer-specific survival ► DFS ► OS ► Disease progression (eg, upstaging, change in proposed treatment)	► Outcomes not directly correlated to timeliness
Studies	► Any interventional or observational study ► Published January 2012–present	► Not available in English language ► Abstract only ► No original data reported

DFS, disease-free survival; NSCLC, non-small cell lung cancer; OS, overall survival.

time-to-treatment and clinical outcomes independently, but we are not aware of any previous reviews which have taken such an approach.

This systematic review aims to provide an updated overview of the literature, representative of current lung cancer management, and to identify patient groups most likely to benefit from expedient care. Focussing on secondary care pathways, we examine factors which may predict the greatest need for rapid investigation and treatment, the size of their impact on outcomes and how best to structure lung cancer services in order to optimise delivery of care.

METHODS

The protocol for this review was registered prospectively and is available online through PROSPERO (International Prospective Register of Systematic Reviews; ID 99239). Reporting standards are in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[14] with methodology and interpretation based on existing frameworks for narrative synthesis conduct.[15 16]

Search strategy

Search strategies were devised for Medline, EMBASE and Cochrane with initial searches performed in July 2018 (online supplemental table 1A–C). Reference lists for included studies and previous reviews were hand-searched for additional relevant studies. Online registries (www.ClinicalTrials.gov and www.isrctn.com) were searched for works unpublished or in-progress. Searches were repeated on 6 October 2020 to capture interval publications.

Full inclusion and exclusion criteria are listed in table 1. Time intervals of interest included any from primary care referral to first treatment receipt, encompassing the 'secondary care' intervals as defined in the Aarhus statement.[17] Studies published prior to January 2012 were excluded in order to minimise differences between reported data and current clinical practice, including routine use of positron emission tomography for staging, introduction of targeted therapies[18 19] and staging from the International Association of Lung Cancer seventh[20] or eighth edition.[21]

Analysis

Themes for subgroup analysis were agreed a priori between the authors HH and NN, including demographics (age, gender, ethnicity and socioeconomic factors), clinical factors (comorbidities, symptoms and performance status), histological subtype, stage and treatment modality. Data were tabulated from all included studies to include: population, sample size, study design and data source, measured time intervals, definitions of 'delay' and outcome measures (online supplemental table 2).

Following abstraction, studies were categorised according to relevance to the above themes. Methodological parameters including reported time intervals, definition of delays and reported outcome measures were compared for any studies reporting data relevant to a specific subgroup, but heterogeneity between studies precluded quantitative analyses. Overall findings are explored in a narrative synthesis with trends summarised via vote counting according to direction of effect.[15] Analyses were defined under the following terms:

- 'Timely care' or 'timeliness' described any aspect of care delivered within a time interval which was shorter than that experienced by a comparatively 'delayed' group, including differences in median time intervals or time intervals falling within a predefined threshold (eg, within a defined number of weeks or a guideline-defined target).
- 'Timeliness advantageous'—faster measured time intervals associated with improved outcomes
- 'Timeliness deleterious'—faster measured time intervals associated with worse outcomes
- 'Mixed'—trends of varying direction of effect reported within different subgroups of one study
- 'Non-significant'—no statistically significant trends reported

Study outcomes are described under the above terms for observed trends as per the primary outcome of the study. Where different subgroups of interest are explored within the narrative synthesis, the reported trends reflect the observed association within that subgroup only.

Bias assessment

Studies were assessed for potential sources of bias, including completeness and clarity of data sources and methodology, representativeness of the target population, management of missing data, defined time intervals and consideration of confounding factors including potential 'waiting time bias' (online supplemental table 5A-B). Bias assessment criteria were derived from the Strengthening the Reporting of Observational Studies in Epidemiology[22] and Aarhus statements,[17] and previous similarly structured reviews.[12 23] For interventional trials, the 2011 Cochrane 'Risk of bias' tool was used.[24]

Study selection and characteristics

Literature search outcomes are summarised in online supplemental figure 1. Searches for unpublished works found two further trials, one withdrawn (ClinicalTrials.gov: NCT1946490) and the second currently recruiting (NCT03535766). Thirty-seven papers met the criteria for inclusion, of which all but five[25–29] included findings relevant to a subgroup of interest. One paper could not be obtained for review of the full manuscript.[30]

RESULTS

We report an overview of the included studies, with subsequent exploration of predefined themes: demographics, clinical factors, histology and stage/treatment. Two interventional papers are then considered separately: one randomised controlled trial (RCT) and one 'quasi-experimental' case–control study.

Overview of included studies

All but two of the included papers are observational. Ten report data from Europe (four from the UK), 19 from North America, 5 from Asia, 1 from Australasia and 2 from South America. Sixteen were single-centre studies, 4 were multicentre studies and 16 report registry data. One reports both an analysis of registry data and a single-centre cohort study.[31]

Timeliness measures are variably defined as dichotomous (15 papers), categorical (8 papers), continuous (19 papers) or guideline concordant versus non-concordant (5 papers). Twenty-four papers include measures of the defined time intervals (online supplemental figure 2). Thirty studies report survival as an outcome measure, 10 report upstaging and 3 report change in treatment intent. Overall, timely care was reported as advantageous in 13 papers, deleterious in 9 and non-significant or mixed in 15 (online supplemental table 2).

Demographics

Five studies focus on demographic factors in their primary analyses.[32–37] Di Girolamo *et al* report all age groups to experience worse survival with receipt of guideline-concordant care compared with those receiving delayed treatment.[32] Three other papers report data on patients aged >66 years only with varied conclusions. Nadpara *et al* examines trends in both regional and national registry datasets, concluding timely care to be independently associated with worse survival in the former[34] but finding no significant association in the latter.[33] Gomez *et al* similarly included only participants aged >66, concluding timeliness to be advantageous in early-stage disease but more equivocal in regional and advanced disease.[36]

Forrest *et al*[35] examine the impact of socioeconomic position (SEP), concluding lower SEP groups to be independently associated with worse survival; however, the authors attribute this to inequalities in performance status and treatment type rather than receipt of timely care. Napolitano *et al* explore the impact of private versus Medicare insurance in a US single-centre cohort (n=112), reporting faster times from diagnostic CT to surgery in those with private insurance (66 vs 86 days, p=0.03); however although there was a trend towards fewer privately insured patients being upstaged, this did not meet statistical significance (22.9% vs 31.8%, p=0.32).[37]

A further nine papers include multivariable analyses controlling for factors including age,[27 31 35 38–42] gender,[27 38–40 42] ethnicity,[31 39 40 42] income,[31 38 40] deprivation index[42] and education,[40] but adjusting for these factors did not influence the reported associations between timeliness and outcomes.

Clinical features and comorbidities

Only one study addresses symptomatology at presentation.[42 43] Redaniel *et al*[42] examine the impact of 'alert' clinical features (haemoptysis, stridor or superior vena cava obstruction), observing an independent association between improved survival and longer time to diagnosis only in those without such symptoms. Several other studies report outcomes in multivariable analyses controlling for clinical factors including comorbidity scores[27 31 35 36 41 42] and performance status.[27 44] Of these, the only significant association is reported by Radzikowska *et al*, who find timeliness associated with worse survival only in patients with performance status of 2 (HR: 1.28, p<0.001).[44]

Histology

Seven papers control for histology in multivariable analysis, but none report this to be a significant factor.[27 28 35 39 42 45 46] Only Murai *et al*'s study of patients referred for stereotactic ablative radiotherapy (SABR) reports a significant association, with higher rates of upstaging seen in those with squamous cell differentiation (29%) versus adenocarcinoma (5%) in patients waiting longest.[47]

Stage

Twenty-six papers stratify outcomes by disease stage (table 2). In addition, four papers report multivariable analyses controlling for stage among other factors, and found no significant impact.[27 34 35 42]

Localised disease

'Localised' disease outcomes are reported in 23 papers including three which group all stage I–IIIA treated with curative intent. Fourteen report outcomes without differentiation by treatment modality (online supplemental table 3A) including two studies reporting rates of upstaging in patients referred for SABR, but not the outcome of SABR delivery per se.[41 47] Twelve studies report outcome data specific to patients undergoing surgery (online supplemental table 3D). Four studies include data for both all treatment modalities and surgical subgroups, and are therefore listed in both tables.

Where all treatment modalities in localised disease are included, the majority of studies find timeliness to be advantageous[36 40 47–52] (including one RCT,[52] discussed below), or do not meet statistical significance.[33 39 41 53 54] Abrao *et al* find timeliness only to be advantageous in those with stage II disease.[46] Only Di Girolamo *et al* demonstrated persistent association between timeliness and worse outcomes in stage I and II disease.[32] Outcomes specific to surgery recipients are discussed below.

Regional disease

Twelve studies refer to either 'regional' or stage III disease in isolation, with more equivocal trends in observations (online supplemental table 3B). Two studies report timeliness to be advantageous,[49 51] four find timeliness to be deleterious in one or more measured time interval,[32 33 50 53] five find no significant association[36 39 46 55 56] and one reports mixed trends across different measures of delay.[57] Robinson *et al* find a significant proportion of patients experience clinical deterioration impacting their treatment intent, but wait times were no different to those with no significant deterioration.[55] Wai *et al* find patients receiving radical chemoradiotherapy rather than palliative interventions experienced faster times from diagnosis to cancer centre referral, but longer intervals between oncology review and first treatment.[57] However, in this paper a significant proportion of controls do not have data for performance status, purportedly a factor used for matching case to control.

Advanced disease

Outcomes in advanced disease (stage IV) are reported by eight studies, of which the only group seen to benefit from timely care are those described in the study by Gomez *et al*[36] as surviving >12 months from diagnosis (online supplemental table 3C). One paper reports no significant association,[51] otherwise

Table 2 Summary of evidence by stage–

	Timeliness advantageous	Non-significant	Timeliness deleterious	Mixed
Localised disease				
All treatment	Murai *et al* 2012[47]	Nadpara *et al* 2015 (I)[33]	Vinod *et al* 2017 (palliative only)[53]	**Di Girolamo *et al* 2018 (I)**[32]
	Wang *et al* 2012 (I–III)[48]	Bullard *et al* 2017 (I)[39]	**Di Girolamo *et al* 2018 (II)**[32]	
	Gomez *et al* 2015 ('Localised')[36]	Frelinghuysen *et al* 2017[41]		
	Navani 2015 (I–IIIA)[52]	Vinod *et al* 2017 (I–II)[53]		
	Kasymjanova *et al* 2017 (I–IIB)[49]	Abrao *et al* 2018 (I)[46]		
	Abrao *et al* 2018 (II)[46]	Ha *et al* 2018 (I–IIIA)[54]		
	Khorana *et al* 2019 (I–II)[40] *			
	Cushman *et al* 2020 (I–II)[50] *			
	Tsai *et al* 2020 (I–II)[51]			
Surgery only	**Yun *et al* 2012**[59]	Coughlin *et al* 2015 (I)[45]		
	Kanarek *et al* 2014 (I–IIIA)[66]	Samson *et al* 2015 (single centre)[31]		
	Bott *et al* 2015 (I)[58] *	Shin *et al* 2013 ('Local')[38]		
	Coughlin *et al* 2015 (II)[45]	Navani *et al* 2015 (I–IIIA)[52]		
	Samson *et al* 2015 (registry)[31] *	Vinod *et al* 2017[53]		
	Yang *et al* 2017 (IA)[67] *			
	Khorana *et al* 2019 (I+II)[40] *			
	Huang *et al* 2020 (stage I)[62]			
	Cushman *et al* 2020 (stage I–IIIA)[50] *			
Regional disease	Kasymjanova *et al* 2017[49]	**Gomez *et al* 2015**[36]	Nadpara *et al* 2015[33]	Wai *et al* 2012[57]
	Tsai *et al* 2020[51]	Robinson *et al* 2015[55]	Vinod *et al* 2017[53]	Di Girolamo *et al* 2018[32]
		Friedman *et al* 2016[56]		
		Bullard *et al* 2017[39]		
		Abrao *et al* 2018[46]		
Advanced disease	**Gomez *et al* 2015 (survival >1 year)**[36]	**Tsai *et al* 2020**[51]	Nadpara *et al* 2015[33]	
			Gomez *et al* 2015 (survival <1 year)[36]	
			Kasymjanova *et al* 2017[49]	
			Vinod *et al* 2017[53]	
			Bullard *et al* 2017[39]	
			Abrao *et al* 2018[46]	
			Di Girolamo *et al* 2018[32]	

Bold denotes papers with n>1000.
Disease stage/subgroup in parenthesis.
*Papers reporting data from NCDB.
NCDB, National Cancer Database.

trends support a deleterious effect of timeliness, though only one paper controls for treatment modality.[53]

Treatment

Surgery

Twelve papers report surgical outcomes, nine concluding timeliness to be advantageous, primarily large studies reporting registry data (online supplemental table 3D). Of note, five of these studies use registry data from National Cancer Database (online supplemental table 4), raising potential for individual patient data to be replicated between studies, particularly those of Samson *et al* and Bott *et al*.[31 58]

RCT evidence from Navani *et al* did not show statistical significance for the association between timeliness and survival in a subgroup of 29 patients treated surgically (HR: 0.37, 95% CI: 0.1 to 1.32).[52] Two relatively small studies are similarly inconclusive[38 53] and a third reports timeliness to only be of significance in patients with stage II disease (vs stage I).[45] Yun *et al* report significantly increasing impact of surgical delays for those treated at low-volume surgical centres.[59] Only one study found a potential increase in risk of upstaging with timeliness, however there was no associated increased risk of mortality in the same cohort.[31]

Systemic therapy and palliative care

Delays of >45 days from diagnosis to receipt of chemoradiotherapy were associated with improved survival versus timely treatment with HR 0.88 (0.83–0.93) in one study.[50] Vinod *et al* note a statistically significant trend towards worse outcomes in those with stage I–III disease receiving palliative care faster, but did not find significant trends for any other treatment modality.[53] No papers were found which report outcomes from targeted therapies or immunotherapy.

Interventional trials

One RCT[52] and one 'quasi-experimental' case–control study[60] were identified. The multicentre Lung-BOOST trial[52]

randomised 133 patients (96 with latterly confirmed stage I–IIIA NSCLC) to endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or conventional diagnosis and staging (CDS). Time to treatment decision in the EBUS-TBNA group was significantly faster that the CDS group (median 15 vs 30 days, p<0.0002). In a post-hoc analysis, longer median survival was observed (503 vs 312 days, p=0.038) in the EBUS-TBNA group versus CDS, though the authors suggest this may in part be attributable to increased pre-operative mediastinal staging resulting in a refined population undergoing surgery, conferring a survival benefit.

Selva *et al*[60] evaluated the impact of a 'rapid diagnosis and treatment programme' against usual care (control data taken from retrospective records). Although introduction of the pathway reduced the diagnosis-to-treatment interval by 9 days, in multivariate analysis this difference was not significant, and no significant difference in stage distribution was observed.

DISCUSSION

Summary of evidence

The trends seen in these observational studies plus one RCT suggest timeliness is of importance in patients with lung cancer with early-stage disease, particularly those undergoing surgery. In advanced disease, the available evidence supports the previously described 'waiting-time bias', accounted for by both urgency of intervention in those who are most symptomatic and palliative interventions being typically delivered more rapidly than curative following confirmed diagnosis.[32] Isolated studies suggest patients with performance status of 2 (57) or squamous cell cancer as compared with adenocarcinoma[59] may benefit disproportionately from expedited care, but these findings are not observed consistently.[41]

Outcomes in early-stage disease are not consistent across the reviewed evidence. Di Girolamo *et al*'s 2018 review of UK cancer registry data reports the impact of receiving care within standard national targets,[61] concluding a harmful impact of faster treatment across all stages of NSCLC in spite of excluding those who died within 90 days of diagnosis. One explanation offered is that treatments delivered fastest—palliative care, active monitoring or 'patient refusal'—confer a worse prognosis. We note 17.6% of those with stage I disease did not receive any active treatment which may account for some degree of the observed association. Data as regards the outlier values within the longest treatment intervals are not presented by Di Girolamo *et al*, but a possibility is that those with indolent lesions who undergo substantial periods of surveillance between initial radiological 'diagnosis' and treatment may also skew the data to suggest that longer times to treatment improve outcomes as has been reported elsewhere.[62–64]

Evidence quality and potential bias

Of the available evidence many studies are observational in design, and only one RCT is identified (online supplemental table 5A,B). Several studies rely on registry data which may be limited in terms of completeness and representativeness,[65] furthermore time interval measures may be extrapolated from indirect sources (eg, dates of insurance claims for consultations). Equally, smaller studies may not be sufficiently powered to detect mortality signals. The reporting of delayed versus timely care is highly variable across the included studies, thus creating difficulty in establishing comparative trends (online supplemental table 2). It is worth noting that many studies report the impact of a binary definition of treatment defined a priori, given the approach taken towards quantifying delays can in itself lead to inconsistency in reported trends.[66]

Substantial efforts in this study have been made to ensure completeness of the literature review and multiple papers not included in previous systematic reviews have been identified. The review protocol, including research questions and thematic analyses, were devised a priori with the aim of minimising reporting bias during narrative synthesis. No issues were encountered as regards accessing studies potentially appropriate for inclusion, but we have not sought individual patient data from the authors of any included studies. We did not find a significant number of works in progress or withdrawn to suggest publication bias to be a significant issue. We note the degree of overlap between some large registry-based studies,[31 40 58 67] which may bias the overall weight of evidence particularly in surgical recipients; however, the contributions taken by different groups in their approach to these data are informative in our subgroup analyses and therefore warrant inclusion.

Generalisability

The presented data cover a broad spectrum of practice, both by geography, healthcare models and time, though there are some limitations to this. The available data are predominantly from North American and European populations, with lesser representation of South American and Asian data and no studies found reporting outcomes from African cohorts. However a number of studies report data controlling for ethnicity and none find this to influence associations with timeliness. Despite our described restrictions on publication date, some included studies report data from >20 years ago, encompassing a period of variation in clinical practice, staging iterations and treatment guidelines.[31 44 57] The structure of the patient pathway from symptoms to treatment varies internationally and we recognise some of the described diagnostic pathways may not be applicable to all systems (eg, direct referral from primary care to thoracic surgery[37]). However, while these differences preclude meaningful quantitative analyses, the relatively consistent trends observed suggest our overall conclusions are likely to be valid across the majority of current healthcare settings.

Two key patient groups are not addressed: those receiving targeted therapies and immune checkpoint inhibitors and those diagnosed via LDCT screening pathways. Cancers diagnosed via LDCT screening programmes may be more indolent and therefore warrant separate consideration,[68] but we found no studies which address timeliness in the management of such lesions in secondary care. Similarly, only two studies mention patients receiving targeted therapies, now widely recognised as standard of care in many patients with advanced disease.[49 53] Timeliness may be key to reduce the risk of clinical deterioration precluding these treatments, but we have not found an evidence base to address this question. Equally, the additional time required for mutational analysis prior to patients receiving these therapies could also contribute to an apparently protective impact of longer diagnostic intervals if treatment modality is not controlled for.[53]

Implications for practice and policy

Our observations from the available evidence suggest that patients referred for surgery may benefit most from shorter times to intervention. The available data are not consistent enough to recommend specific time intervals, but at worst a prognostic impact may be seen with delays of just 7 days from diagnosis to treatment[51] with other studies suggest a cumulative impact

of worse prognosis with every week's delay from diagnosis to treatment.[40 66]

These findings suggest that the targets laid out in the National Optimal Lung Cancer Pathway, targeting a 'referral-to-diagnosis' interval of 28 days and 'referral-to-treatment' of 49 days,[69] will give rise to a downstream improvement in NSCLC survival particularly for those with early-stage disease. The impact for those with advanced disease is less certain; our conclusions highlight the overwhelming impact of confounding factors on observed trends in this group, and further work is required to appreciate the role of timeliness as regards the risk of clinical deterioration and subsequent impact on emergency admissions or planned treatments.

For all stages of disease, other factors warrant consideration in determining targets for optimal delivery of care. Timely care may reduce anxiety and improve overall patient experiences for many, though equally may contribute to a sense of bewilderment and complexity for some.[70] Equally, pressure to deliver surgery within a certain timeframe may limit opportunity for 'prehabilitation' and smoking cessation and thus impact resection rates and post-operative outcomes in high-risk patients.[71–73]

CONCLUSION

Although there are inconsistencies and limitations to the available evidence, the observed trends support timeliness as being associated with better outcomes in patients with early-stage disease, particularly those undergoing surgery. In patients with advanced disease, the benefit of urgent intervention is likely to be outweighed by other clinical and biological factors. Currently, evidence is lacking as regards the role of timeliness for patients receiving targeted therapies or immunotherapy, or those diagnosed via lung cancer screening programmes. Rapid pathways to treatment should be implemented to improve outcomes for patients with early-stage lung cancer.

Author affiliations
[1]Lungs for Living Research Centre, UCL Respiratory, UCL, London, UK
[2]Barts Health Knowledge and Library Services, Barts Health NHS Trust, London, UK
[3]MRC Clinical Trials Unit at UCL, UCL, London, UK
[4]Department of Respiratory Medicine, Barts Health NHS Trust, London, UK
[5]Centre for Primary Care and Public Health, Queen Mary University of London, London, UK
[6]School of Population Health and Environmental Sciences, King's College London, London, UK
[7]XX Place Health Centre, London Borough of Tower Hamlets, London, UK
[8]Centre for Cancer Outcomes, North Central and North East London Cancer Alliances, University College London Hospitals NHS Foundation Trust, London, UK
[9]Department of Respiratory Medicine, University of Leicester, Leicester, UK
[10]Department of Thoracic Medicine, University College London Hospital, London, UK

Twitter William M Ricketts @tb_doc and Neal Navani @LungConsultant

Contributors All authors contributed to the design of the review. HH and NN led work on writing the protocol, undertaking literature review and analysis, AT devised the strategies for database searches and SB and DF advised on methodology, EM designed and compiled figure 2 in the Supplement. All authors contributed to and approved the final manuscript.

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ORCID iDs
Helen Hall http://orcid.org/0000-0001-7305-8367
Sarah Burdett http://orcid.org/0000-0001-8687-2851
William M Ricketts http://orcid.org/0000-0002-0475-0744
Sam M Janes http://orcid.org/0000-0002-6634-5939
Neal Navani http://orcid.org/0000-0002-6412-7516

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Title: Association between time-to-treatment and outcomes in non-small cell lung cancer: a systematic review

Authors:

Helen K Hall, Adam Tocock, Sarah Burdett, David Fisher, William Ricketts, John Robson, Thomas Round, Sarita Gorolay, Emma MacArthur, Donna Chung, Sam M Janes, Michael D Peake, Neal Navani

Online Supplementary materials

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Table 1a: Database search methodology – outcomes of first search (Medline)

1. ((lung* AND (carcinogen* OR sarcom* OR metasta* OR tumor* OR tumour* OR 2arcinoma* OR cancer* OR neoplasm*)) AND diagnos*).ti,ab	47802
2. Exp *"LUNG NEOPLASMS"/ AND exp *DIAGNOSIS/	22558
3. Exp *"LUNG NEOPLASMS"/di	15129
4. (44 OR 45 OR 46)	72249
5. Exp *"TIME FACTORS"/	2019
6. Exp *"TIME-TO-TREATMENT"/	1557
7. (delay* OR timely OR timeliness OR speed*).ti,ab	616523
8. (("2 week*" OR "two week*") ADJ wait*) OR 2ww OR tww).ti,ab	234
9. (48 OR 49 OR 50 OR 51)	619407
10. (47 AND 52)	1899
11. (outcome*).ti,ab	1392388
12. Exp "PATIENT OUTCOME ASSESSMENT"/	5386
13. (70 OR 71)	1393537
14. (survival).ti,ab	802667
15. Exp MORTALITY/	342122
16. (mortality).ti,ab	634887
17. (73 OR 74 OR 75)	1474956
18. (72 OR 76)	2540309
19. (53 AND 77)	696

Table 1b: Database search strategy – outcomes of first search (EMBASE)

1. ((lung* AND (carcinogen* OR sarcom* OR metasta* OR tumor* OR tumour* OR 2arcinoma* OR cancer* OR neoplasm*)) AND diagnos*).ti,ab	85332
2. Exp *"LUNG CANCER"/ AND exp *DIAGNOSIS/	18020
3. Exp *"LUNG CANCER"/di	21226
4. (54 OR 55 OR 56)	106387
5. (delay* OR time* OR timeliness).ti	344301
6. (("2 week*" OR "two week*") ADJ wait*) OR 2ww OR tww).ti,ab	565
7. Exp "TIME FACTOR"/	19038
8. (58 OR 59 OR 60)	361215
9. (57 AND 61)	1409
10. (outcome*).ti,ab	2039908
11. Exp "TREATMENT OUTCOME"/	1396119
12. (79 OR 80)	2806681
13. (survival).ti,ab	1167404
14. (mortality).ti,ab	922767
15. Exp SURVIVAL/	941339
16. Exp MORTALITY/	941184
17. (82 OR 83 OR 84 OR 85)	2379942
18. (81 OR 86)	4473764
19. (62 AND 87)	627

Table 1c: Database search strategy – outcomes of first search(Cochrane)

#1 (((lung* AND (carcinogen* OR sarcom* OR metasta* OR tumor* OR tumour* OR 3arcinoma* OR cancer* OR neoplasm*)) AND diagnos*)):ti,ab,kw 5094
#2 MeSH descriptor: [Lung Neoplasms] explode all trees 6733
#3 MeSH descriptor: [Diagnosis] explode all trees 312508
#4 #2 and #3 3251
#5 MeSH descriptor: [Lung Neoplasms] explode all trees and with qualifier(s): [diagnosis – DI] 275
#6 #1 or #4 or #5 7504
#7 MeSH descriptor: [Time Factors] explode all trees 62064
#8 MeSH descriptor: [Time-to-Treatment] explode all trees 237
#9 (delay* OR timely* OR timeliness OR speed*):ti,ab,kw 57111
#10 ((("2 week" or "2 weeks" OR "two week" or "two weeks") and wait*) OR 2ww OR tww):ti,ab,kw 567
#11 #7 or #8 or #9 or #10 114955
#12 #6 and #11 650
#13 (outcome*):ti,ab,kw 496294
#14 MeSH descriptor: [Patient Outcome Assessment] explode all trees 553
#15 #13 or #14 496302
#16 survival or mortality 155298
#17 MeSH descriptor: [Survival] explode all trees 128
#18 #16 or #17 155298
#19 #15 or #17 496348
#20 #12 and #19 391
#21 #20 with Cochrane Library publication date from Jan 2012 to present 258

Figure 1: PRISMA flowchart

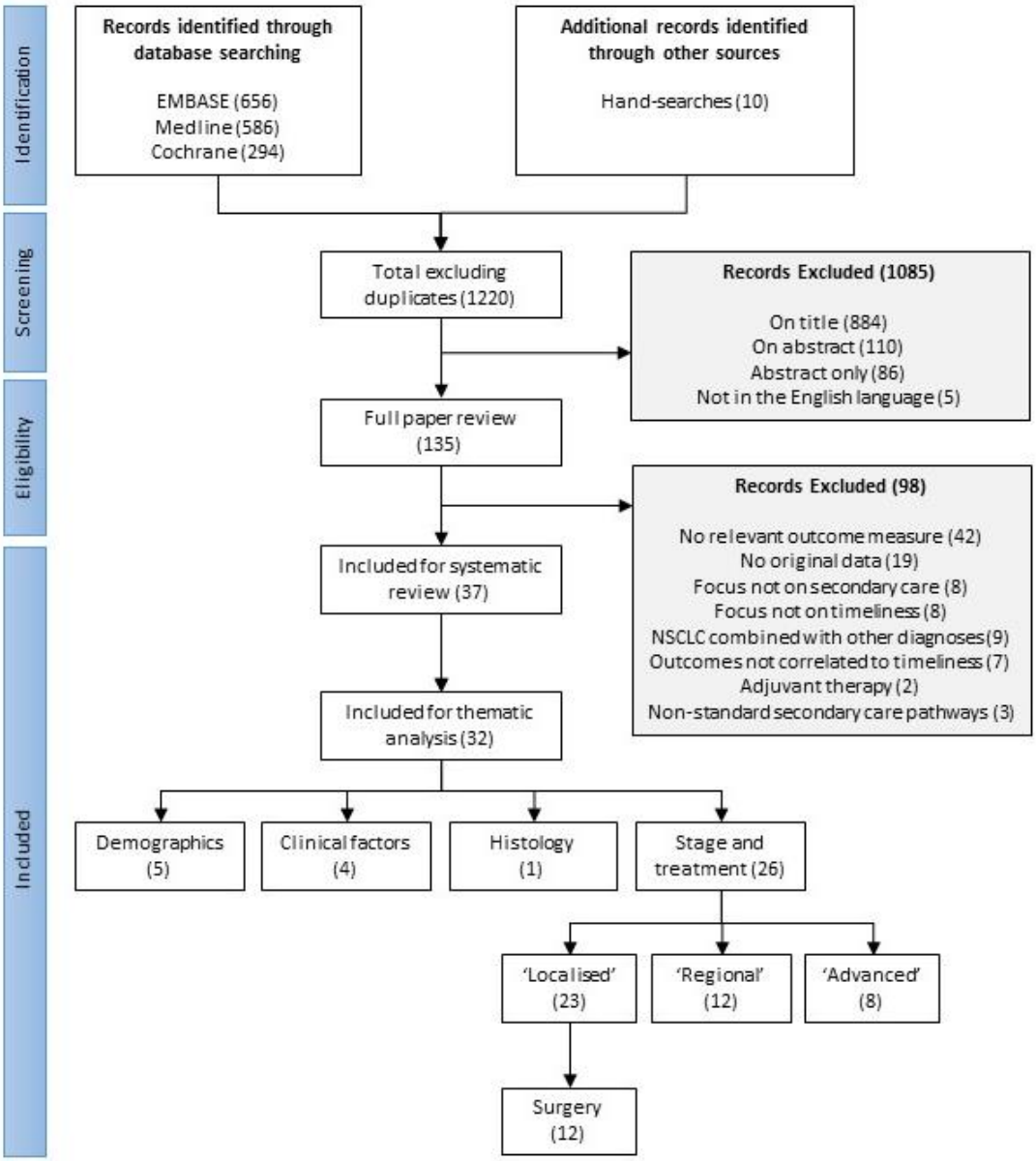


Table 2: Summary and abstraction of included studies

Reference	Population and NSCLC* sample size	Design and data source	Measured time intervals	Outcome measure	Trend (overall)	Results summary	Sub-group analysis
Abrao 2017(25) Brazil	All LC, previously untreated n=435	Single centre, observational cohort study 2008-2014	First review to diagnosis, diagnosis to treatment	LC-specific survival	Timeliness deleterious	Worse LC-specific survival seen in those with <1.5 months from diagnosis to first treatment in multivariate analysis (13 vs 4 months, p<0.01).	Nil
Abrao 2018(46) Brazil	All NSCLC n=359	Single centre, observational cohort study 2008 - 2014	Diagnosis to treatment	OS	Timeliness deleterious	Overall intervals of >2 months from diagnosis to treatment was protective, with adjusted HR 0.75 (p=0.001)	Stage (localised, regional, advanced)
Bott 2015(56) USA	Clinical stage 1 NSCLC undergoing curative resection n=55,653	Registry (NCDB) 1998 - 2010	Histological diagnosis to surgery	Pathological upstaging	Timeliness advantageous	A delay of >8 weeks from diagnosis to surgery was associated with higher risk of pathological upstaging (OR 1.10)	Stage (localised), surgery
Brocken 2012(26) Netherlands	All consecutive referrals to a single centre lung MDT (indeterminate nodules excluded) n=261	Single centre, observational cohort study 1999 - 2009	PC referral to first review; first review to diagnosis; PC referral to treatment; diagnosis to treatment	PFS, OS	Non-significant	Delays not associated with disease stage or survival	Nil
Bullard 2017(39) USA	All NSCLC n=746	Registry (South Carolina Central Cancer Registry) 2005-2010	Diagnosis to treatment	OS	Timeliness deleterious	Worse survival seen with diagnosis to treatment intervals of <6 weeks in advanced disease	Stage (localised, regional, advanced)
Coughlin 2015(45) Canada	Clinical stage I-II NSCLC undergoing surgical resection n=222	Single centre, observational cohort study 2010 - 2011	Treatment decision to treatment	Pathological upstaging	Timeliness advantageous	In stage 2 disease, delays of >8 weeks were associated with increased risk of pathological upstaging and worse survival. Did not meet significance in stage 1 disease.	Stage (localised), surgery
Cushman 2020(52) USA	Histologically confirmed stage I-IIIB NSCLC treated with curative intent, excluding time to treatment >365 days n=140,455	Registry (NCDB) 2004 - 2015	Diagnosis to treatment	OS	Timeliness advantageous	>45 days from diagnosis to treatment associated with median survival 61.5 months vs 70.2 for timely care (p < 0.001)	Stage (localised, regional), surgery

Di Girolamo 2018(67) UK	All NSCLC n=121,963	Registry (CWT, NCRAS) 2009 - 2013	PC referral to first review; diagnosis to treatment; PC referral to treatment	One-year net survival (adjusted for competing causes of mortality)	Timeliness deleterious	One-year survival worse in those treated within 31- and 62-day targets	Demographics, stage (localised, regional, advanced)
Forrest 2015(35) UK	All lung cancer, any active treatment. n=12,152	Registry (Lung Cancer Audit; Northern and Yorkshire Cancer Registry and Information Centre; Hospital Episode Statistics) 2006-2009	PC referral to first review; diagnosis to treatment; PC referral to treatment	OS	Timeliness deleterious	Treatment within 31 days of diagnosis was associated with worse 2-year survival (OR 0.37)	Demographics
Frelinghuysen 2017(41) Netherlands	Inoperable NSCLC planned for SABR n=123	Single centre, observational cohort study 2005 - 2008	Diagnostic CT to treatment planning CT (ISI) Excl if ISI <25 days	Upstaging, OS	Non-significant	Risk of upstaging was not correlated to longer time to treatment	Stage (localised)
Friedman 2016(62) USA	All stage III NSCLC n=109	Single centre case:control, comparing referral to single clinician versus cancer board	First clinical review to treatment	OS	Non-significant	Patients seen by MTD experienced faster treatment with borderline significant improved median survival (14 vs 17 months, p = 0.054)	Stage (regional)
Geiger 2014(29) USA	Non-metastatic NSCLC n=47	Single centre, observational cohort study 2009 – 2011	Diagnostic CT to treatment planning CT (ISI) Excl if ISI >120 days	Upstaging Change in treatment plan	Non-significant	Upstaging observed in 21% of those with ISI <43 days vs 30% of those with ISI >43 days, p = not given	Nil
Gomez 2015(36) USA	All NSCLC with Medicare claims n=28,732	Registry (Medicare claims) 2004 - 2007	Diagnosis to treatment	OS	Mixed	Treatment within 35 days of diagnosis associated with improved survival in those with localised disease and those with advanced disease who survived >1 year (HR 0.86 for both groups) but worse in those with advanced disease surviving <1 year (HR 1.35)	Demographics, stage (localised, regional, advanced)
Gonzalez-Barcala 2014(27) Spain	Pathologically confirmed LC n=262	Single centre, observational cohort study 2005-2008	First review to diagnosis, diagnosis to treatment	Survival NOS	Timeliness deleterious	Survival is improved in patients waiting >61 days from diagnosis to treatment, but time from first review to diagnosis was not significant.	Nil

Ha 2018(51) USA	Stage I-IIIA NSCLC treated with curative intent n=177	Single centre, observational cohort study 2010 - 2017	Tumour board meeting to treatment initiation	PFS, OS	Non-significant	HR 1.0 (p=0.56) for overall survival in stage I-IIIA HR 1.0 (p=0.74) for DFS in stage I only	Stage (localised)
Huang 2020(59) Taiwan	Clinical stage I adenocarcinoma undergoing surgery n=561	Single centre, observational cohort study 2006 – 2016	Radiological diagnosis to surgery (RDS) Histological diagnosis to surgery (HDS)	OS	Non-significant Timeliness advantageous	No significant difference in 5 year survival between timely vs delayed RDS Timely HDS associated with improved 5 year survival, with HR 2.031 in multivariable model	Stage (localised), surgery
Kanarek 2014(55) USA	Stage I-II NSCLC, undergoing resection n=174	Single centre, observational cohort study 2003 - 2009	Diagnosis to surgical review, surgical review to treatment, diagnosis to treatment	Survival	Timeliness advantageous	Each week of delay from diagnosis to surgery increases HR by 1.04, adjusting for age, stage (IIB) and tumour size.	Stage (localised), surgery
Kasymjanova 2017(50) Canada	All NSCLC receiving active treatment, inc targeted therapies n=593	Single centre, observational cohort study 2010 - 2015	PC referral to first review; diagnosis to treatment; PC referral to treatment. Others treatment specific.	Survival	Timeliness advantageous	Delays >30 days from diagnosis to treatment associated with worse median survival (11 vs 14.8 months, p=0.04).	Stage (localised, regional, advanced)
Khorana 2019(40) USA	All stage 1-2 NSCLC, excluding those without treatment or with delay >180 days n=363,863	Registry (NCDB) 2004 - 2013	Diagnosis to treatment	OS	Timeliness advantageous	Longer time to treatment associated with worse OS in stage 1 and 2 disease undergoing surgery	Stage (localised), surgery
Murai 2012(47) Japan	Stage 1 NSCLC undergoing SABR n=201	Multicentre prospective cohort study (sub-analysis) 2004-2010	Diagnostic CT to treatment planning CT	Upstaging	Timeliness advantageous	Delays >4 weeks from diagnosis to planning CT are associated with increased upstaging (21% vs 0%).	Histology, stage (localised),
Nadpara 2015(33) USA	All LC diagnoses age >66 years, from Medicare claims and SEER registry n=42,089	Registry (SEER-Medicare) 2002 - 2007	CXR to first review; PC referral to first review; diagnosis to treatment; PC referral to treatment	Survival	Timeliness deleterious	Median survival 281 (271-291) vs 500 (479 - 520) days for timely vs delayed care. Overall survival reported as NSCLC vs SCLC, but not broken down by stage	Demographics, stage (localised, regional, advanced)

Nadpara 2016(34) USA	Medicare beneficiaries aged >66 diagnosed with LC, care stratified as per clinical guidelines n=1641	Registry (West Virginia Cancer Registry-Medicare) 2003-2006	CXR to first review; PC referral to first review; diagnosis to treatment; PC referral to treatment	Survival	Timeliness deleterious	Overall median survival no different in those receiving timely vs delayed care (299 vs 467 days, p=0.3), similar when stratified by stage and histology. However adjusted lung cancer mortality lower amongst patients receiving delayed care (HR 0.75, p<0.05), but full data not given.	Demographics
Napolitano 2020(37) USA	Histologically confirmed NSCLC referred for surgery n = 112	Single centre, observational cohort study 2013 – 2016	Time from first detection on CT to surgical resection	Upstaging	Non-significant	No significant difference between risk of upstaging in private vs Medicare insured (p=0.3), despite longer wait times for Medicare insured cohort	Demographics
Navani 2015(57) UK	All radiological stage I-IIIA lung cancers, randomised to EBUS vs usual care for first diagnostic test n=96	Multicentre RCT 2008 - 2011	First review to treatment decision	Survival	Timeliness advantageous	EBUS group experienced shorter time to treatment plan and improved median survival	Stage (localised), surgery
Radzikowska 2012(44) Poland	Histologically confirmed NSCLC, any treatment modality n=6384	Registry (Register of the National Tuberculosis and Lung Diseases Research Institute) 1995-1998	PC referral to first review; first review to first procedure; first review to diagnosis; diagnosis to treatment	OS	Timeliness deleterious	Secondary care delays <52 days associated with worse overall survival (HR 1.18, p=0.001)	Clinical factors
Redaniel 2015(42) UK	All lung cancer diagnoses, defined by presence or absence of NICE 'alert' symptoms n=5737*	Registry (Clinical Practice Research Datalink; Merged Cancer Registry; HES; ONS) 1998-2009	PC presentation to diagnosis	Survival	Mixed	Worse survival with intervals from first presentation to diagnosis of <1 month versus >6 months for patients without 'alert' symptoms, but no significant association in patients where 'alert' symptoms were present	Clinical factors
Robinson 2015(61) Canada	All biopsy confirmed stage 3 NSCLC n=237	Single centre, observational cohort study 2008 - 2012	Abnormal CT to oncology consultation; respiratory consultation to oncology consultation	Change in treatment intent	Non-significant	Patients who experienced weight loss or decline in performance status which resulted in a palliative approach to treatment did not have delayed care	Stage (regional)

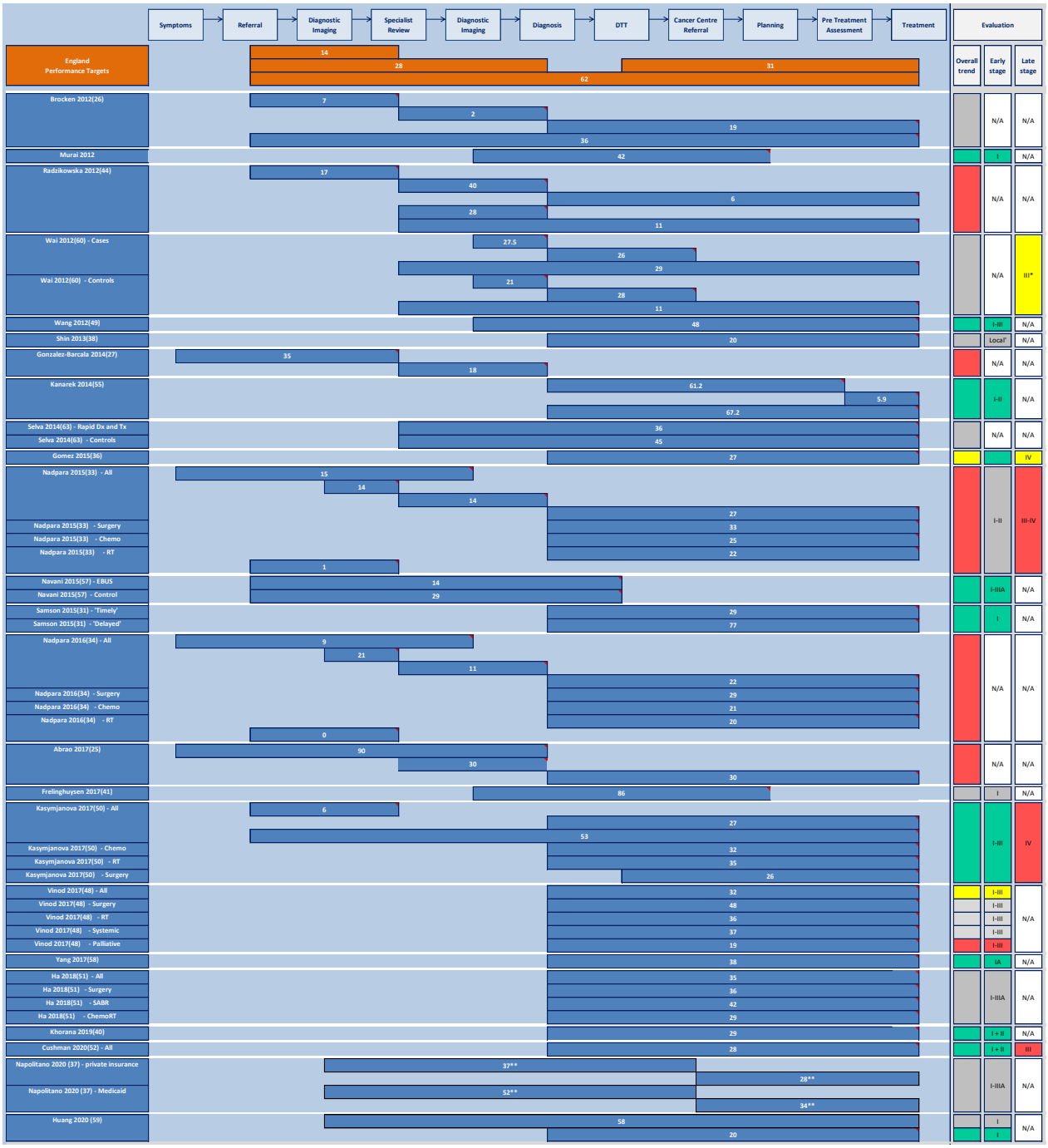
Samson 2015(31) USA	All clinical stage 1 NSCLC undergoing surgery n=27,022	Single centre, observational case:control study plus registry (NCDB) 1998 - 2010	Diagnosis to treatment	Pathological upstaging, survival	Timeliness advantageous	Delays of ≥8 weeks from diagnosis to surgery associated with higher risk of pathological upstaging and reduced median survival.	Stage (localised), surgery
Selva 2014(63) Spain	All NSCLC diagnosed either via rapid access referral route or (retrospective) via standard pathway n=362	Single centre, 'quasi-interventional' case:control study 2005 - 2009	First secondary care appt booked to first treatment Diagnosis to treatment interval	Upstaging	Non-significant	Rapid access reduced time to treatment but did not achieve a stage shift.	Intervention
Shin 2013(38**)** South Korea	Histologically confirmed LC undergoing primary surgery n=398	Registry (Korean Central Cancer Registry) 2006 - 2011	Diagnosis to treatment	OS	Non-significant	No association between time to surgery (<1 to >12 weeks) and all-cause mortality	Stage (localised), surgery
Tsai 2020(53) Taiwan	Histologically confirmed NSCLC receiving active treatment n=42,962	Registry (Taiwan Cancer Registry Database) 2004 – 2010	Histological diagnosis to treatment	OS	Mixed	Delays ≥7 days associated with increased relative risk of death in stage 1 (HR 1.45-2.41) and stage II disease (HR 1.21 – 1.58), but only significant for delays of >60 days in stage III, and non-significant for stage IV.	Stage (localised, regional, advanced)
Vinod 2017(48) Australia	All NSCLC (any treatment) n=1729	Registry (South Western Sydney Local Health Central Cancer Registry) 2006 - 2012	Diagnosis to treatment	Survival	Mixed	In patients with stage 3-4 NSCLC only, or stage 1-2 referred for palliative care, there was a marginal trend towards better survival in those who waited longer for treatment (mortality HR 0.99, p<0.05)	Stage (localised, regional, advanced), surgery, palliative
Wai 2012(60) Canada	Unresectable stage 3 NSCLC n=357	Case:control (2:1 radical vs palliative treatment intent) 1990-2000	First abnormal test to diagnosis; diagnosis to oncology referral; oncology review to treatment	Treatment intent	Non-significant	No significant difference between time to oncologist assessment and treatment intent.	Stage (regional)
Wang 2012(49) USA	Inoperable stage 1-3 NSCLC with serial pre-treatment PET/CT scans n=34	Multi-centre observational cohort study 2003 - 2010	First CT/PET to first treatment	Upstaging, PFS, OS	Timeliness advantageous	Inter-scan interval > 58 days associated with higher rates of progression (46.2% vs 4.8%, p=0.007). Tumour growth rates and TTT were not associated with OS or PFS.	Stage (localised)

Yang 2017(58) USA	Stage 1A squamous cell carcinoma undergoing surgery n=4984	Registry (NCDB) 2006 - 2011	Diagnosis to treatment	Survival	Timeliness advantageous	Worse 5-year survival in those waiting >38 days from diagnosis to treatment	Stage (localised), surgery
Yun 2012(54) South Korea	All lung cancer patients undergoing curative surgery n=9097*	Registry (Korean Central Cancer Registry) 2001 - 2005	Diagnosis to treatment	Survival	Timeliness advantageous	Treatment delay >1 month associated with worse survival, particularly in low/medium volume centres	Stage (localised), surgery
Živković 2014(28) Montenegro	All lung cancers diagnosed via single centre with >12 months follow up data available n=151	Single centre, observational cohort study 2009	PC referral to first review; first review to diagnosis	Upstaging, survival	Non-significant	No association between time from referral to treatment and disease stage or survival.	Nil

(*) denotes total study sample size, where NSCLC forms an unspecified subgroup

CT = computed tomography; CWT: Cancer Waiting Times; EBUS = endobronchial ultrasound; HES = Hospital Episode Statistics; HR; hazard ratio; ISI = interscan interval; LC: lung cancer; MDT; multidisciplinary team; NCDB = National Cancer Database; NCRAS = National Cancer Registration and Analysis Service; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; ONS = Office for National Statistics; OS = overall survival; PC = primary care; PET = positron emission tomography; PFS = progression free survival; RCT: randomised controlled trial; TTT: Time to treatment; UK: United Kingdom; US = United States of America

Figure 2: Reported median time intervals for included studies



	Timeliness advantageous
	Mixed
	Timeliness deleterious
	Non-significant
	Not applicable

Chemo = chemotherapy; DTT = Decision To Treat; Dx = diagnosis; EBUS = endobronchial ultrasound, NOLCP = National Optimal Lung Cancer Pathway; RT = Radiotherapy; SABR = Stereotactive ablative radiotherapy; Tx = Treatment

*Wai 2012: Mixed associations observed for different time intervals between case and control groups
** Values reported as mean

Table 3a: Summary of evidence in early disease (*excludes studies only reporting surgical data, see Table 3d*)

	Study	Study design	Stage	Treatment	n	Time interval	Delay definition	Outcome measure	Trend	Outcome
ALL TREATMENT MODALITIES										
STAGE I only	Murai 2012(47)	Observational cohort (multi-centre)	I	Referred for SABR	201	Diagnostic CT to SABR planning CT	Interscan interval >4 weeks	Upstaging	Timeliness advantageous	Risk of upstaging 20.8% vs 0% (p=0.003) for delayed vs timely care.
	Nadpara 2015(33)	Observational cohort (registry)	I	Surgery, radiotherapy or chemotherapy	3,478	Diagnosis to treatment	>8 weeks from diagnosis to surgery >7 weeks from diagnosis to chemotherapy >6 weeks from diagnosis to radiotherapy	Lung cancer specific mortality	Non-significant	3yr survival rate 0.62 (0.6 - 0.64) vs 0.58 (0.55 - 0.62) for timely vs delayed
	Bullard 2017(39)	Observational cohort (registry)	'Localised'	Surgery, chemotherapy or radiotherapy	185	Diagnosis to treatment	>42 days	Median survival	Non-significant	HR for mortality 0.98 (p=0.94) for timely vs delayed
	Frelinghuysen 2017(41)	Observational cohort	I	Referred for SABR	117	Diagnostic CT to SABR planning CT	NA	Upstaging, survival	Non-significant	Median ISI no different between stable T1, upstaged T1 and stable T2 lesions (p=0.4)
	Abrao 2018(46)	Observational cohort (single centre)	I	Any	30	Diagnosis to treatment	> 8 weeks	All-cause mortality	Non-significant	HR 1.24 (0.39-3.98, p=0.71) for delayed vs timely treatment
	Di Girolamo 2018(32)	Observational cohort (registry)	I	Any	6,158	GP referral to first review	>14 days	1 year net survival	Non-significant	88.8% (CI 87.9-89.7) vs 84.8% (78.7 - 91.0)
					15,363	Diagnosis to treatment	>31 days		Timeliness deleterious	89.3% (88.7 - 89.9) vs 95.6% (94.0 - 97.3)
					5,932	GP referral to treatment	>62 days		Non-significant	91.2% (90.1-92.3) vs 93.4% (92.1-94.6)
	Khorana 2019(40)	Observational cohort (registry)	I	Any	280,175	Diagnosis to treatment	>6 weeks	Overall survival	Timeliness advantageous	HR 1.032 (1.031-1.034, p<0.001) for each week delay

	Cushman 2020(52)	Observational cohort (registry)	I	Surgery, chemotherapy or radiotherapy	95,378	Histological diagnosis to treatment	>45 days	Overall survival	Timeliness advantageous	HR 1.15 (HR 1.12 – 1.17) for delayed vs timely
	Tsai 2020(53)	Observational cohort (registry)	I	Surgery, chemotherapy or radiotherapy	5,681	Histological diagnosis to treatment	Categorical (≤7 days, 8-14, 15-60, ≥61 days)	Overall survival	Timeliness advantageous	HR 1.45-2.41 for all intervals versus ≤7 days (p<0.001 for all)
STAGE II only	Nadpara 2015(33)	Observational cohort (registry)	II	Surgery, radiotherapy or chemotherapy	766	Diagnosis to treatment	>8 weeks from diagnosis to surgery >7 weeks from diagnosis to chemotherapy >6 weeks from diagnosis to radiotherapy	Lung cancer specific mortality	Non-significant	3yr survival rate 0.40 (0.36 - 0.45) vs 0.37 (0.30 - 0.44) for timely vs delayed
	Abrao 2018(46)	Observational cohort (single centre)	II	Any	26	Diagnosis to treatment	> 8 weeks	All-cause mortality	Timeliness advantageous	HR 3.08 (1.05 – 9.0, p=0.04) for delayed vs timely
	Di Girolamo 2018(32)	Observational cohort (registry)	II	Any	4,460	GP referral to first review	>14 days	1 year net survival	Non-significant	73.5% (72.1-74.9) vs 76.4% (68.0-84.7) for timely vs delayed
					8,614	Diagnosis to treatment	>31 days		Timeliness deleterious	74.4% (73.4-75.4) vs 86.1% (82.1-90.0) for timely vs delayed
					4,200	GP referral to treatment	>62 days		Timeliness deleterious	76.4% (74.6-78.2) vs 81.0% (78.9-83.0) for timely vs delayed
	Khorana 2019(40)	Observational cohort (registry)	II	Any	83,688	Diagnosis to treatment	>6 weeks	Overall survival	Timeliness advantageous	HR 1.016 (1.014 - 1.018, p<0.001) for each week delay for delayed vs timely
	Cushman 2020(52)	Observational cohort (registry)	II	Surgery, chemotherapy or radiotherapy	22,072	Histological diagnosis to treatment	>45 days	Overall survival	Timeliness advantageous	HR 1.05 (1.01 – 1.09) for delayed vs timely
	Tsai 2020(53)	Observational cohort (registry)	II	Surgery, chemotherapy or radiotherapy	1,526	Histological diagnosis to treatment	Categorical (≤7 days, 8-14, 15-60, ≥61 days)	Overall survival	Timeliness advantageous	HR 1.21-1.58 for all groups versus ≤7 days (p<0.05 for all)

STAGE I-IIIA NOS	Wang 2012(49)	Observational cohort (multi-centre)	I-III	Radiotherapy +/- concurrent chemotherapy	34	Diagnostic PET to treatment planning PET	ISI >58 days	Disease progression and upstaging	Timeliness advantageous	OR for disease progression 1.027 (p = 0.02) in delayed vs timely.
	Gomez 2015(36)	Observational cohort (registry)	'Localised'	Any surgery, radio- or chemotherapy, or combination	7,960	Diagnosis to treatment	> 35 days	All-cause mortality	Timeliness advantageous	HR 0.86 (0.8-0.91, p < 0.01) for timely vs delayed
	Navani 2015(57)	Multi-centre RCT: EBUS vs usual care as first diagnostic test	I-IIIA	All	96	First secondary care review to treatment decision	Intervention (median 15 days) vs control (median 30 days)	Survival	Timeliness advantageous	Median survival 503 days vs 312 days (p=0.038) in intervention vs control
	Kasymjanova 2017(50)	Observational cohort (single centre)	I-IIB	Any active treatment	177	Diagnosis to treatment	>30 days	Survival	Timeliness advantageous	HR for survival 2.07 (1.45-2.97, p<0.001) for timely vs delayed
	Vinod 2017(48)	Observational cohort (registry)	I-II	Any	375	Diagnosis to treatment	NS	Survival	Non-significant	All: HR 1 (1 - 1.01, p=0.25)
			I-III	Radiotherapy	288				Non-significant	Radiotherapy: HR 0.99 (p=0.11)
				Palliation	148				Timeliness deleterious	Palliative: HR 0.99 (0.98-0.99, p=0.02) for timely vs delayed
	Ha 2018(51)	Observational cohort (single centre)	I-IIIA	Surgery, radiotherapy, chemotherapy, combination or none	177	Tumour board meeting to treatment initiation	Guideline concordance	Overall survival	Non-significant	HR 1.0 (p=0.56) for survival
			I		122			Disease-free survival		Disease free survival in stage 1 subgroup (HR 1.0, p=0.74)

CT = computed tomography; GP = general practitioner (primary care); HR = hazard ratio; ISI = interscan interval; PET = positron emission tomography; SABR = stereotactic ablative radiotherapy

Table 3b: Summary of evidence in regional disease

Study	Study design	Stage	Treatment	n	Time interval	Delay definition	Outcome measure	Trend	Outcome
Wai 2012(60)	Case control (registry)	III	Chemoradiotherapy	119	Diagnosis to cancer centre referral	NA	Treatment intent	Timeliness advantageous	Median duration 26 days vs 28 days for radical CRT recipients vs palliative Tx, p=0.035
					Diagnosis to oncology consult			Non-significant	Median duration 31 days vs 31.5 days for radical CRT recipients vs palliative Tx, p=0.264
			Palliative	238	Oncologist review to start of treatment			Timeliness deleterious	Median duration 29 days vs 11 days for radical CRT recipients vs palliative, p <0.0001
Gomez 2015(36)	Observational cohort (registry)	'Regional'	Any surgery, radio- or chemotherapy, or combination	8,962	Diagnosis to treatment	> 35 days	All-cause mortality	Non-significant	HR 1.05 (0.8 - 0.91, p=0.054) for timely vs delayed treatment
Robinson 2015(61)	Observational cohort (single centre)	III	Radical vs palliative (any)	237	CT imaging to oncology consultation	NA	Treatment intent	Non-significant	No association between median time intervals and clinical deterioration impacting treatment intent
					Respiratory review to oncology review				
Nadpara 2015(33)	Observational cohort (registry)	III	Surgery, radiotherapy or chemotherapy	5,291	Diagnosis to treatment	>8 weeks from diagnosis to surgery	Lung cancer specific mortality	Timeliness deleterious	Median survival 305 days (*291 - 317) vs 472 days (443 - 498) for timely vs delayed treatment = * = 95% CI
						>7 weeks from diagnosis to chemotherapy			
						>6 weeks from diagnosis to radiotherapy			
Friedman 2016(62)	Observational cohort (single centre)	III	Any	109	First clinical review to treatment	NA	Overall survival	Non-significant	Patients seen by cancer board versus single clinician experienced faster treatment with borderline significant improved median survival (14 vs 17 months, p = 0.054)
Kasymjanova 2017(50)	Observational cohort (single centre)	III	Any active treatment	111	Diagnosis to treatment	>30 days	Overall survival	Timeliness advantageous	Median survival 17.2 vs 32.7 months for delayed vs timely treatment (p=0.04)

Bullard 2017(39)	Observational cohort (registry)	'Regional' II-III	Surgery, chemotherapy or radiotherapy	232	Diagnosis to treatment	>42 days	Survival	Non-significant	HR for mortality 1.18 (p=0.41) for timely vs delayed
Vinod 2017(48)	Observational cohort (registry)	III	Any	422	Diagnosis to treatment	NA	Survival	Timeliness deleterious	HR for mortality 0.99 (95% CI 0.99 – 0.99, p=0.03) for delayed vs timely
Abrao 2018(46)	Observational cohort (single centre)	III	Any	73	Diagnosis to treatment	> 8 weeks	All-cause mortality	Non-significant	HR 0.65 (0.38 - 1.1, p=0.11) for delayed vs timely treatment
Di Girolamo 2018(32)	Observational cohort (registry)	III	Any	14,453	GP referral to first review	>14 days	1 year net survival	Non-significant	48.1% (47.3-49.0) vs 46.2% (41.2-51.3)
				23,667	Diagnosis to treatment	>31 days		Timeliness deleterious	53.9% (53.3-54.6) vs 74.5% (69.7-79.2)
				12,495	GP referral to treatment	>62 days		Non-significant	52.4% (51.3-53.4) vs 65.2% (63.5-67.0)
Cushman 2020(52)	Observational cohort (registry)	III	Surgery, chemotherapy or radiotherapy	23,005	Histological diagnosis to treatment	>45 days	Overall survival	Timeliness deleterious	HR 0.93 (0.89-0.96) for delayed vs timely
Tsai 2020(53)	Observational cohort (registry)	III	Surgery, chemotherapy or radiotherapy	11,696	Histological diagnosis to treatment	Categorical (≤7 days, 8-14, 15-60, ≥61 days)	Overall survival	Timeliness advantageous	HR 1.13 for delays ≥61 days versus ≤7 days (p = 0.001)

CI = confidence interval; CRT = chemoradiotherapy; HR = hazard ratio; Tx = treatment

Table 3c: Summary of evidence in advanced disease

Study	Study design	Stage	Treatment	n	Time interval	Delay definition	Outcome measure	Trend	Outcome (timely vs delayed)
Nadpara 2015(33)	Observational cohort (registry)	IV	Surgery, radiotherapy or chemotherapy	7,212	Diagnosis to treatment	>8 weeks from diagnosis to surgery >7 weeks from diagnosis to chemotherapy >6 weeks from diagnosis to radiotherapy	Lung cancer specific mortality	Timeliness deleterious	Median survival 146 days (CI 140 - 152) vs 290 days (270-308) for timely vs delayed treatment
Gomez 2015(36)	Observational cohort (registry)	'Distant'	Surgery, radiotherapy or chemotherapy	11,810	Diagnosis to treatment	> 35 days	All-cause mortality (for those with survival <1 year vs >1 year)	Timeliness deleterious	HR 1.35 (1.28 - 1.42, p<0.001) for timely vs delayed treatment in patients surviving <1 year
								Timeliness advantageous	HR 0.86 (0.74-0.99, p=0.042) for timely vs delayed treatment in patients surviving ≥1 year
Kasymjanova 2017(50)	Observational cohort (single centre)	IV	Any active treatment	390	Diagnosis to treatment	>30 days	All-cause mortality	Timeliness deleterious	HR 0.72 (0.58-0.92, p = 0.008) for delayed vs timely treatment
Vinod 2017(48)	Observational cohort (registry)	IV	Any	878	Diagnosis to treatment	NS	Survival	Timeliness deleterious	HR for mortality 0.99 (95% CI 0.99 – 0.99, p=0.0008) for delayed vs timely
Bullard 2017(39)	Observational cohort (registry)	'Distant'	Surgery, radiotherapy or chemotherapy	329	Diagnosis to treatment	>6 weeks	Survival	Timeliness deleterious	HR for mortality 2.2 (p<0.001) for timely vs delayed
Abrao 2018(46)	Observational cohort (single centre)	IV	Any	230	Diagnosis to treatment	>8 weeks	All-cause mortality	Timeliness deleterious	HR for mortality 0.48 (0.35-0.66, p<0.001) for delayed vs timely
Di Girolamo 2018(32)	Observational cohort (registry)	IV	Any	22,460	GP referral to first review	>14 days	1 year net survival	Non-significant	23.3% (22.8 - 23.9) vs 19.5% (16.1-22.9)
				31,442	Diagnosis to treatment	>31 days		Timeliness deleterious	33.8% (33.2-34.3) vs 52.6% (45.0-60.2)
				14,665	GP referral to treatment	>62 days		Timeliness deleterious	33.8% (33.0-34.7) vs 44.6% (42.6-46.7)
Tsai 2020(53)	Observational cohort (registry)	IV	Surgery, chemotherapy or radiotherapy	24,059	Histological diagnosis to treatment	Categorical (≤7, 8-14, 15-60, ≥61 days)	Overall survival	Non-significant	No significant association between any delay and survival

GP = general practitioner; HR = hazard ratio

Table 3d: Summary of evidence in surgical cohorts

	Study	Study design	Stage	n	Time interval	Delay definition	Outcome measure	Trend	Outcome
SURGERY ONLY									
STAGE I only	Bott 2015(56)	Observational cohort (registry)	I	55,653	Diagnosis to treatment	>8 weeks	Pathological upstaging	Timeliness advantageous	HR 1.1 for upstaging (p=0.002) for delayed vs timely treatment
	Coughlin 2015(45)	Observational cohort (single centre)	I	180	Treatment decision to surgery	Categorical (months)	Upstaging	Non-significant	OR 0.216 (p=0.07) for delays of ≥3 months vs <1 month
							Survival		HR 1.064 (p=0.92) for delays of ≥3 months vs <1 month
	Samson 2015(31)	Case:control (registry)	I	13,511 'delayed'	Diagnosis to treatment	> 8 weeks	Survival, upstaging	Timeliness advantageous	Upstaging from clinical T1 significantly more likely in delayed vs timely (p=0.002)
				13,511 'timely'					Median survival 69.9 (+/- 1.3) months vs 57.7 (+/- 1.0) months for timely vs delayed, HR 1.004 per week delay
	Samson 2015(31)	Case:control (single centre)	I	449 'delayed'	Diagnosis to treatment	> 8 weeks	Upstaging	Timeliness deleterious	25% vs 16% for timely vs delayed (p=0.001)
				522 'timely'			Survival	Non-significant	Median survival 97.5 months (0.2-168.6) vs 90.5 (0-172.8)
	Yang 2017(58)	Observational cohort (registry)	IA	4,984	Diagnosis to treatment	>38 days	5 year survival	Timeliness advantageous	HR for death at 5 years 1.13 (1.02 – 1.25) in delayed vs timely care
	Khorana 2019(40)	Observational cohort (registry)	I	193,058	Diagnosis to treatment	>6 weeks	OS	Timeliness advantageous	HR 1.024 (1.022-1.026, p<0.001) for each week delay
	Huang 2020(59)	Observational cohort (single centre)	I	561	Radiological diagnosis to surgery (RDS)	>60 days	OS	Non-significant	5 year survival 83.3% vs 83.7% for timely vs delayed RDS (p = 0.57)
					Histological diagnosis to surgery (HDS)	>21 days		Timeliness advantageous	5 year survival 85.5% vs 75.9% for timely vs delayed HDS (p = 0.003). HR 2.031 in multivariate analysis.
STAGE II only	Coughlin 2015(45)	Observational cohort (single centre)	II	42	Treatment decision to surgery	Categorical (months)	Upstaging	Timeliness advantageous	OR 2.0 (p=0.02) for delays of ≥2 months vs <1 month
							Survival		HR 3.6 (p=0.036) for delays of ≥2 months vs <1 month

	Khorana 2019(40)	Observational cohort (registry)	II	49,386	Diagnosis to treatment	>6 weeks	OS	Timeliness advantageous	HR 1.017 (1.014-1.021) for each week delay
STAGE I-IIIA/NOS	Yun 2012(54)	Observational cohort (registry)	NS	9,094	Diagnosis to treatment	>31 days	5-year survival	Timeliness advantageous	HR 1.16 (1.06 - 1.27) for survival in timely vs delayed
	Shin 2013(38)	Observational cohort (registry)	'Local'	191	Diagnosis to treatment	>12 weeks	All-cause mortality	Non-significant	HR 0.79 (CI 0.42 – 1.48) for delays up to 12 weeks vs any shorter interval.
	Kanarek 2014(55)	Observational cohort (single centre)	I-IIA	174	Diagnosis to treatment	>42 days	Survival	Timeliness advantageous	HR 1.04 (CI 1.00 – 1.09) for each week's delay in surgery for stage I-II disease
	Navani 2015(57)	Multi-centre RCT	I-IIIA	29	First secondary care review to treatment decision	Intervention (median 15 days) vs control (median 30 days)	Survival	Non-significant	HR 0.37 (p=0.125) for survival in intervention vs control
	Vinod 2017(48)	Observational cohort (registry)	I-III	246	Diagnosis to treatment	NS	Survival	Non-significant	HR 1.01 (p=0.48) for timely vs delayed
	Cushman 2020(52)	Observational cohort (registry)	I-III	85,267	Histological diagnosis to treatment	>45 days	Overall survival	Timeliness advantageous	HR 1.14 (1.11 – 1.16) for delayed vs timely

HR = hazard ratio, NS = non-significant; OS = overall survival; RCT = randomised controlled trial

Table 4: Comparison of studies utilising National Cancer Database (NCDB)

Study	Years	Inclusion criteria	Exclusion criteria	Primary outcome measure
Bott 2015(56)	1998 – 2010	Clinical stage I NSCLC undergoing resection	Patients with T2b disease	Pathological upstaging
Samson 2015(31)	1998 – 2010	Clinical stage I NSCLC matched case:control for delayed vs timely surgery	Nil specified	Overall survival
Khorana 2019(40)	2004 – 2013	Stage I-II NSCLC (alongside other cancers)	No treatment received; first treatment >180 days from diagnosis; unable to establish treatment intervals; uncommon histology	Overall survival
Cushman 2020(52)	2004 – 2015	Non-metastatic NSCLC, treated with curative intent	Metastatic or unidentified stage' palliative treatment only; chemotherapy or immunotherapy alone; no treatment received; unknown treatment interval; first treatment >365 days from diagnosis	Overall survival
Yang 2020(58)	2006 - 2011	Clinical stage IA squamous cell carcinoma, undergoing lobectomy	Adjuvant chemo/radiotherapy; patients having surgery the same day as diagnosis (latterly included in sensitivity analysis)	Overall survival

Table E8a: Assessment of bias (observational studies)

1a. Are eligibility criteria, sources and methods of participant selection and follow-up clearly described? **1b.** Is the study population likely to be representative of the target population?
2a. Are demographic and characteristic data provided and complete? **2b.** Are reasons for non-participation included?
3a. Are missing data measured and accounted for?
4a. Are definitions for both time-intervals and outcome measures defined *a priori*? **4b.** Are the definitions appropriately measurable?
5a. Are statistical methods described? **5b.** Are confounding factors controlled for? **5c.** Is there consideration of potential waiting-time paradox?

Reference	1a.	1b.	2a.	2b.	3a.	4a.	4b.	5a.	5b.	5c.
Abrao 2017 (25)	Yes	Yes	Yes	Yes	Yes	Yes	Some symptom based	Yes	Unclear which	In discussion
Abrao 2018 (46)	Yes	Excluded unresectable disease diagnosed at surgery	Yes	Yes	NA	Yes	Yes	Yes	Yes	In discussion
Bott 2015 (56)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Brocken 2012 (26)	Yes	Excluded stage IV	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bullard 2017 (39)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	In discussion
Coughlin 2015 (45)	Yes	Yes	Yes	NA	Some	Yes	Yes	Yes	Yes	NA
Cushman 2020 (52)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Di Girolamo 2018 (32)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Some	Yes
Forrest 2015 (35)	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes
Frelinghuysen 2017 (41)	Yes	Excludes treatment within 25 days	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Friedman 2016 (62)	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	No
Geiger 2014 (29)	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	No
Gomez 2015 (36)	Yes	Excludes palliative care	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gonzalez-Barcala 2014 (27)	Yes	Yes	Yes	Yes	Yes	Yes	Some symptom based	Yes	Yes	In discussion
Ha 2018 (51)	Yes	Veterans	Yes	Yes	Yes	Yes	Yes	Yes	Yes	In discussion
Huang 2020 (59)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Kanarek 2014 (55)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	In discussion
Kasymjanova 2017 (50)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Khorana 2019 (40)	Yes	Some exclusions	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	NA
Murai 2012 (47)	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	No
Nadpara 2015 (33)	Yes	Unclear	Yes	Yes	Yes	Yes	Some symptom based	Yes	Yes	Yes
Nadpara 2016 (34)	Yes	Yes	Yes	Yes	NA	Yes	Some symptom based	Yes	Yes but not shown	In discussion
Napolitano 2020 (37)	Yes	Single surgeon only	Yes	No	No	Yes	Yes	Yes	Some	No
Radzikowska 2012 (44)	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes
Redaniel 2015 (42)	Yes	Yes	Yes	Yes	Yes	Yes	Some symptom based	Yes	Yes	Yes
Robinson 2015 (61)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Samson 2015 (31)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	NA
Selva 2014 (63)	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	In discussion
Shin 2013 (38)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	In discussion
Tsai 2020 (53)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vinod 2017 (48)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	In discussion
Wai 2012 (60)	Yes	Yes	Incomplete	Yes	Yes	Yes	Yes	Yes	Yes	No

Wang 2012 (49)	Yes	Some	Yes	Yes	NA	Yes	Yes	Yes	No	No
Yang 2017 (58)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Yun 2012 (54)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Živković 2014 (28)	Yes	Yes	Some	NA	NA	Yes	Some symptom based	Some	Histology	In discussion

Table E8b: Assessment of bias (randomised controlled trials)

	Selection bias		**Performance bias**		**Detection bias**	**Attrition bias**	**Reporting bias**	**Other**
	Random sequence generation	**Allocation concealment**	**Blinding of participants**	**Blinding of personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other source of bias**
Navani 2015 (57)	Yes	Yes	Not possible	Not possible	Yes	No	No	No