NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

The effects of systemic anticancer treatment (SACT) or radiotherapy on risk of severe illness or death in patients with cancer and COVID-19

Rapid evidence review

February 2021

Contents

Background

NICE developed the COVID-19 rapid guidelines: delivery of systemic anticancer treatments (NG161) and delivery of radiotherapy (NG162) jointly with NHS England and NHS Improvement to support the system response to the COVID-19 pandemic. Both guidelines have been undergoing a surveillance process to check that recommendations are up to date, with a regular check of the scientific evidence base for the recommendations.

On 3 June 2020, a prospective UK cohort study (n=800 patients with cancer with a positive SARS-CoV-2 test) was identified: COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments, compared with patients not on chemotherapy (Lee et al). The study indicated that COVID-19 mortality may not be associated with the cancer therapies that cancer patients receive.

During guideline development (in March 2020), expert opinion, early Chinese data, and unpublished modelling indicated that the cancer therapies that cancer patients received may cause poorer outcomes with COVID-19, likely due to immunosuppression.

An independent advisory expert panel was convened to consider this study, alongside a rapid review of other relevant evidence. This document sets out the evidence review and the committee discussion of the evidence in relation to delivery of systemic anticancer treatments (NG161) and delivery of radiotherapy (NG162).

Methodology

A review protocol for the rapid evidence review was developed, quality assured at NICE and finalised with feedback from the expert panel (see appendix 1).

Focused searches for evidence were undertaken by NICE's information services team up to 6 July 2020 (see appendix 2). Studies were also considered from the NICE surveillance checks up to 13 July 2020 for completion of the draft evidence review for expert panel meeting 1 on 23 July 2020. Potentially relevant studies identified in surveillance checks were also assessed for eligibility for inclusion in the

evidence review to 24 September 2020 (see appendix 3 for further details). We also monitored subsequently published evidence emerging from surveillance checks up to 9 December 2020 and no studies were identified that impacted on the guideline recommendations.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the protocol (see appendix 1). One reviewer undertook title and abstract screening with 10% checked by a second reviewer, and all studies requiring a second opinion were considered by a second reviewer.

Full text references of potentially relevant evidence were obtained and reviewed by 1 reviewer to determine whether they met the inclusion criteria for this evidence review. All full text eligibility decisions were checked by a second reviewer. All uncertainties in full text selection were discussed with a second reviewer and referred to a third reviewer if needed. See appendix 3 for the study flow chart of included studies and the list of studies excluded at full text with reasons for exclusion.

All data extraction and risk of bias assessment were performed by 1 reviewer and double checked for accuracy by a second reviewer.

Studies were narratively synthesised due to heterogeneity across studies. Key study characteristics and results were presented in a narrative summary, with evidence tables for each study presented in appendix 4. GRADE profiles were completed for all critical outcomes available in the evidence.

For further details on rapid review process and methods, see NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

Review question

Are patients with cancer and COVID-19 who are receiving/have recently received systemic anticancer treatment (SACT) or radiotherapy at increased risk of severe COVID-19 illness or death?

The review protocol is shown in appendix 1 but a summary is shown below in table 1.

Table 1 Summary of key protocol criteria

Population	All patients diagnosed with cancer and laboratory-confirmed COVID-19
Exposure (prognostic factors)	Patients with cancer who have received SACT or radiotherapy within the 4 weeks preceding a diagnosis of COVID-19
Comparator	Patients with cancer and COVID-19 diagnosis who have not received any SACT or radiotherapy within 4 weeks of COVID-19 diagnosis
Outcomes	Critical outcomes: all-cause mortality, COVID-19-related mortality, cancer-related mortality Other outcomes: severe COVID-19 illness measures; quality of life; length of hospital stay

Summary of the evidence

Included studies

A total of 4 new studies were included, in addition to the 1 study (Liang et al. 2020) which informed the original guideline (developed in March 2020), resulting in a total of 5 studies in this evidence review. See table 2 and table 3 for a brief overview of included studies. More detailed results are presented in the data extraction tables in appendix 4, and GRADE profiles in appendix 5. Please note that there may be some overlap in patient populations included in the Chinese studies (Tian and Zhang), but it is not clear how much overlap due to limited reported details.

Table 2 Overview of included studies – new evidence (to September 2020)

Study	Country, study design, dates	Population (n)	Prognostic factors, timeframe	Control of confounding factors	Main results
Kuderer 2020	USA, Canada, Spain Cohort study, prospective and retrospective, 17 March to 16 April 2020	Patients with active cancer and laboratory confirmed COVID-19 (n=928)	Cytotoxic therapy Non-cytotoxic therapy (targeted therapy, hormone therapy, immunotherapy, radiotherapy) Within 4 weeks of COVID-19 diagnosis	Adjusted for age, sex, smoking status and obesity	No significant difference in all-cause mortality with cytotoxic or non-cytotoxic therapy
Lee 2020a	UK Cohort study prospective, 18 March to 26 April 2020	Patients with active cancer and laboratory confirmed COVID-19 (n=800)	Chemotherapy Immunotherapy Targeted therapy Hormone therapy Radiotherapy Within 4 weeks of COVID-19 diagnosis	All patients: adjusted for age, sex and comorbidities	All patients: no significant difference in all-cause mortality with cancer therapies
Lee 2020b	UK Cohort study prospective, 18 March to 8 May 2020 Follow up of Lee 2020a	Patients with active cancer and laboratory confirmed COVID-19 (n=1044)	Chemotherapy	Patients with haematological cancers: adjusted for age and sex	Patients with haematological cancers: significantly increased all-cause mortality with recent chemotherapy
Tian 2020	China (Wuhan) Cohort study, retrospective, 13 January to 18 March 2020	Adult patients with malignant solid tumours and haematological malignancy and laboratory confirmed COVID-19 (n=232)	Chemotherapy or radiotherapy; targeted therapy or immunotherapy	Adjusted for age, sex, comorbidities tumour stage and cancer type	No significant difference in COVID-19 severity with chemotherapy or radiotherapy; significantly increased odds with targeted therapy or immunotherapy
Zhang 2020	China (Wuhan/Hubei), cohort study, retrospective,	Patients with cancer and laboratory confirmed	Antitumour therapies (chemotherapy radiotherapy	Adjusted for age and sex	There was a significantly higher hazard ratio of severe

Study	Country, study design, dates	Population (n)	Prognostic factors, timeframe	Control of confounding factors	Main results
	January 13 to 26 February 2020	COVID-19 (n=28)	targeted therapy immunotherapy) Within 14 days of COVID-19 diagnosis		events with antitumour therapies

Table 3 Overview of included studies – original guideline evidence (to March 2020)

Study	Country, study design, dates	Population (n)	Prognostic factors, timeframe	Control of confounding factors	Main results
Liang 2020	China, cohort study prospective, data cut-off 31 January 2020	Patients with a history of cancer and laboratory confirmed COVID-19 (n=18)	Chemotherapy or surgery within past month	Adjusted for age, smoking history and comorbidities	Significantly increased odds of severe events with chemotherapy or surgery

Key results

Findings for the impact of anticancer therapies on people with cancer and COVID-19 varied across the included studies. However, there is complexity in interpreting the results and the data must be interpreted in the context of the COVID-19 pandemic. Across the new studies there is a high degree of heterogeneity in how the studies were conducted, which outcomes were reported and over what timeframe, along with the control of confounding factors in the studies. There was also variation in how studies reported and grouped the following: types of systemic anticancer treatment (SACT), types and stages of cancers, comorbidities, and treatments for COVID-19. As such, the data must be carefully considered in terms of quality and generalisability to the UK context; only 1 study was UK based (Lee et al. 2020).

The 2 largest studies (Lee et al. 2020a and Kuderer et al. 2020) did not find that SACT or radiotherapy received within the 4 weeks preceding a COVID-19 diagnosis affected all-cause mortality in people with cancer. However, a further subgroup analysis by Lee et al. (2020b) showed a significantly increased risk of all-cause

mortality in people with haematological malignancy who had recent chemotherapy compared with people with haematological malignancy who had not had recent chemotherapy. The studies were based in the UK (Lee et al. 2020), and the USA, Canada and Spain (Kuderer et al. 2020).

The 2 smaller studies (Tian et al. 2020 and Zhang et al. 2020) were based in China and may have had some overlap in patient populations (but this is unclear due to limited reported details). These studies found less certain effects of SACT, with a trend towards an increased risk of severe COVID-19 outcomes with SACT.

Subgroups

In line with the review protocol, subgroups by type of SACT (chemotherapy, radiotherapy, immunotherapy and targeted therapy), along with radiotherapy and hormone therapy are discussed below. GRADE profiles for all studies reporting all-cause mortality (a critical outcome) are available in appendix 5.

Chemotherapy

There is low to very low confidence that receiving chemotherapy within 4 weeks of COVID-19 diagnosis does not affect all-cause mortality in patients with cancer and COVID-19. This is based on 2 studies, with the number of patients exposed to chemotherapy totalling 441. See GRADE profile 1 (appendix 5).

There is low confidence that receiving chemotherapy within 4 weeks of COVID-19 diagnosis significantly increases all-cause mortality in patients with haematological cancer and COVID-19. This is based on 1 study, with the number of patients exposed to chemotherapy totalling 108. See GRADE profile 1 (appendix 5).

Radiotherapy

There is low confidence that receiving radiotherapy within 4 weeks of COVID-19 diagnosis does not affect all-cause mortality in patients with cancer and COVID-19. This is based on 1 study, with the number of patients exposed to radiotherapy totalling 76. See GRADE profile 2 (appendix 5).

Immunotherapy

There is low confidence that receiving immunotherapy within 4 weeks of COVID-19 diagnosis does not affect all-cause mortality in patients with cancer and COVID-19. This is based on 1 study of 44 patients exposed to immunotherapy. See GRADE profile 3 (appendix 5).

Targeted therapy

There is low confidence that receiving targeted therapy within 4 weeks of COVID-19 diagnosis does not affect all-cause mortality in patients with cancer and COVID-19. This is based on 1 study, with the number of patients exposed to targeted therapy totalling 72. See GRADE profile 4 (appendix 5).

Hormone therapy

There is low confidence that receiving hormone therapy within 4 weeks of COVID-19 diagnosis does not affect all-cause mortality in patients with cancer and COVID-19. This is based on 1 study of 64 patients exposed to hormone therapy. See GRADE profile 5 (appendix 5).

Other subgroups

It was not possible to undertake subgroup analysis of specific cancer drug regimens or cancer types because few studies reported this detail, and when they did, patient numbers were too small. However, some studies did look at other factors and subgroups associated with increased severity or mortality with COVID-19 (please see the data extraction tables in appendix 4 and original publications for full details). The subgroup results from the 2 largest studies are briefly described below.

- The UK cohort study (Lee et al. 2020a; n=800) found that mortality in patients with cancer and COVID-19 is primarily driven by older age and the presence of other non-cancer morbidities. The study found no significant difference in patients receiving palliative chemotherapy versus no chemotherapy or no treatment, but there was a significant difference with non-palliative chemotherapy versus palliative chemotherapy (OR 0.40, 95% CI 0.17 to 0.96; p=0.040; Lee et al. 2020a). No significant difference in primary location of the underlying cancer with recent chemotherapy versus no chemotherapy was identified in their initial

analyses (Lee et al. 2020a). However, further analyses (Lee et al. 2020b) showed that people with haematological cancers who had chemotherapy within 4 weeks of COVID-19 presentation (n=108) had significantly increased all-cause mortality compared with people with haematological cancers who had not had chemotherapy within 4 weeks of COVID-19 presentation (n=119).

- Lee et al. (2020b) also compared adults with cancer and COVID-19 in the UK Coronavirus Cancer Monitoring Project (UKCCMP) cohort with a non-COVID-19 UK cancer control group (UK Office for National Statistics 2017 data) to determine the effects of tumour subtype and demographics on prevalence and mortality from COVID-19. Patients with COVID-19 and cancer were more likely to be men. Some tumour subtypes were found to be over-represented in the UKCCMP registry compared with the non-COVID-19 cancer control group; for example, people with haematological cancers were more at risk of COVID-19. However, some cancer types were under-represented in the UKCCMP registry; for example, lung cancer and prostate cancer. All-cause mortality in people with cancer and COVID-19 was significantly associated with increasing age and male sex. In multivariable analysis adjusting for age and sex, patients with leukaemia had significantly increased mortality compared with the rest of the UKCCMP cohort. People with haematological cancers (n=227) were significantly more likely to need high-flow oxygen, non-invasive ventilation and ICU admission for ventilation, and significantly more likely to have a more severe disease course than people with non-haematological cancers (n=817) in the UKCCMP cohort.
- The CCC19 cohort study (Kuderer et al. 2020; n=928) found that several factors were associated with increased mortality within 30 days in patients with cancer and COVID-19, notably: age, sex, 2 or more comorbidities, and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or more. There was no difference in 30-day mortality based on type of tumour. There was evidence that a cancer status of present (both progressing or stable) or unknown was associated with worse 30-day mortality, compared with remission.

Evidence strengths and limitations

This review specifically sought to address the issue of whether people with cancer and COVID-19 who are receiving or have recently received systemic anticancer treatment (SACT) or radiotherapy are at an increased risk of severe illness or death. The review protocol limited eligibility to cohort studies and case-control studies that controlled for age, and systematic reviews of these study types, to focus on study types that would address the review question. The review found that more evidence was available than at the time of guideline development (March 2020). In March 2020, the only evidence available was 1 small (n=18) Chinese cohort study (Liang et al. 2020), unpublished modelling and expert consensus.

However, given COVID-19 is an emerging disease and the fact that only observational data are available, the included studies all have some degree of bias and confounding. The risk of bias of each study is shown as part of the data extraction tables in appendix 4, with GRADE profiles for all-cause mortality in appendix 5.

The key areas of uncertainty across the evidence base are:

- The sample sizes are relatively small, especially for specific anticancer therapies, and so the subgroups are underpowered to detect meaningful differences in mortality and severity of COVID-19 for cancer therapies.
- Whether the patients who received cancer therapies 4 weeks before being diagnosed with COVID-19 were somehow different to those who did not receive cancer therapies during this time.
- Whether patients could switch regimens to less immunosuppressive regimens.
- Whether there are specific cancer types or specific regimens that affect severity and mortality with COVID-19, because patient numbers are too small to provide meaningful subgroup results.
- A lack of data in children.
- An editorial commenting on the 2 cohort studies (by Lee et al, 2020 and Kuderer et al, 2020) has highlighted the short follow up times and high proportions of

missing data in these analyses, as well as lack of clarity on cancer stage and status (Poortmans et al. 2020).

- In non-UK studies, there is uncertainty whether the patients and treatments they received (both cancer therapies and COVID-19 treatments) are representative of UK clinical practice. It has already been noted in the literature that the generalisability of Chinese data to Europe and North America is problematic because there are differences in terms of prevalence of cancer types, the settings in which SACT is delivered, and the fact that severe complications from COVID-19, including mortality, may be higher in some European countries, than in China, for unknown reasons (Oh et al. 2020).

Within the UK cohort study (Lee et al. 2020a, 2020b) the following additional issues were noted:

- The authors noted that there may have been a selection bias because patients not receiving chemotherapy may have stopped therapy due to poorer performance status (Lee et al. 2020a).
- Patients receiving end of life care, patients in hospices, and patients living in nursing homes are unlikely to be reported or included in the registry (Lee et al. 2020b).
- Performance status, patient comorbidity scale or index, and ethnicity data were not initially collected and so could not be analysed (Lee et al. 2020b).
- There are missing data, notably around cancer stage (25% missing) and comorbidities (15% missing) (Lee et al. 2020a).
- The mortality was 28%, which the authors felt might indicate the severity of symptoms of the cancer patients who chose to seek treatment (Lee et al. 2020a). For comparison, the mortality in the CCC19 cohort was 13% (Kuderer et al. 2020a).
- There was 6% utilisation of intensive therapy units (ITU). Whether this is due to a real difference in intensive bed usage between studies, or the fact that the UK may have utilised other hospital areas for intensive care outside of ITU is unclear (Lee et al. 2020a). For comparison, the intensive care unit (ICU) admittance in the CCC19 cohort was 14% (Kuderer et al, 2020).

- Only 3% of patients were in remission (the reasons are unclear but might reflect the types of patients seeking cancer treatment during the pandemic) (Lee et al, 2020a). In contrast, 45% of patients in the CCC19 cohort were in remission (Kuderer et al, 2020).

Expert panel discussion

The sections below describe how the independent advisory expert panel considered the evidence in relation to the recommendations within the NICE COVID-19 rapid guidelines: delivery of systemic anticancer treatments (NG161) and delivery of radiotherapy (NG162). As there is commonality in the evidence base, there is naturally some overlap in points discussed across the guidelines.

COVID-19 rapid guideline: delivery of systemic anticancer treatments (NG161)

Relative value of different outcomes

When developing the review protocol, the expert panel identified all-cause mortality, COVID-19-related mortality and cancer-related mortality as critical outcomes. The panel discussed these outcomes and agreed that all-cause mortality was likely to be the most critical and reliable outcome, as assigning mortality to COVID-19 or cancer may be less reliable.

The panel discussed the GRADE profiles presented in the evidence review for all-cause mortality. They agreed that there was, on balance, no difference in all-cause mortality with any of the systemic anticancer treatments (SACT) people with cancer received (chemotherapy, targeted therapy, immunotherapy or hormone therapy). However, the UK cohort study (Lee et al. 2020b) indicated that people with haematological malignancies who had recent chemotherapy may be at increased risk of mortality (although it was difficult to know whether this increased risk was due to chemotherapy or was disease related). They noted the uncertainty in evidence (for example, wide confidence intervals in some studies) and that it could not be completely ruled out that cancer therapies did have some impact on COVID-19 severity or mortality. They agreed from the evidence and their clinical experience

that developing severe complications from COVID-19 was likely to be mostly driven by patient age, male sex, comorbidities and severity of cancer, rather than SACT.

The panel also discussed the cancer-specific hazard ratios for hospital admission and mortality due to COVID-19 in the report of the development and validation of the QCOVID living risk prediction algorithm (Clift et al. 2020). The study by Clift et al. (2020) was not considered eligible for the evidence review because in the study anticancer therapies were not received within 4 weeks of COVID-19 diagnosis. However, it is a key UK-specific study that is based on a large dataset and provides cancer-specific hazard ratio data for mortality and hospitalisation. For this reason, the expert panel agreed to consider this study as part of the guideline update. This study was based on the QResearch database (covering 1,205 general practices in England). The data showed increased risks of hospital admission and mortality due to COVID-19 in people who had received chemotherapy in the previous 12 months. The panel discussed the apparent trend in these data for increased risks with increasingly immunosuppressive chemotherapy.

The panel did not feel it was possible to draw definitive conclusions for specific regimens based on current evidence. As such, they felt it important that clinicians consider the risks and benefits for each individual patient and do that in a collaborative way through discussions with the patient.

On balance the panel agreed that the new evidence was sufficient to change the recommendation in NG161 which states: be aware that patients with COVID-19 are at risk of severe disease following systemic anticancer treatment. The recommendation advising when to continue or defer SACT was also considered to require modification. As a result, the guideline was revised. The revised recommendations highlight the need for shared decision making relating to SACT for individual patients based on risks and benefits.

The panel also felt that it was important that all cancer patients, not just those with symptomatic or confirmed COVID-19, are aware of risk factors that might predispose them to severe COVID-19 outcomes. Thus, a new recommendation was added to section 1 of the guideline (communicating with patients and minimising risk) to

ensure that all cancer patients are aware of risk factors that are likely to influence COVID-19 severity and mortality.

A revised recommendation also now reflects the importance of reaching a shared decision on the risks and benefits of changing treatment regimens or having treatment breaks.

The panel also discussed vaccination against COVID-19 as being a factor that would need to be considered when assessing risk and agreed to add this to the revised recommendations.

Quality of the evidence

The certainty of the evidence base was low to very low as rated by GRADE. The panel discussed issues with studies in the evidence review, including small sample sizes, missing data or lack of detail and uncertainty in potential confounding factors (such as whether patients receiving SACT were different from those not receiving SACT).

Nevertheless, the new evidence was considered a step-change in evidence compared to what was available at the time of guideline development (March 2020). In March 2020, the guideline was based on expert opinion, early Chinese data and unpublished modelling.

The panel considered that the 2 largest studies in the evidence review (Lee et al. 2020a and Kuderer et al. 2020) were the most applicable to the UK. The panel noted uncertainties with the UK cohort study (Lee et al. 2020a), particularly around small sample sizes for certain subgroups of SACT and wide confidence intervals around some of the odds ratios. They also recognised that shielding practices in the UK at the time of data collection may have contributed to a selection bias that could impact on the risk of COVID-19 for the cohort.

The panel discussed the use of a 4-week time period in the UK cohort study for patients with COVID-19 (in relation to SACT treatment). On balance it was felt that it was a sensible time period as most treatments are on a 3- to 4-weekly cycle, and mortality following SACT is often measured at 30 days. The panel concluded that a 4

week time period was appropriate for assessing impact, as it would, if anything, overestimate the risks associated with SACT.

The panel considered that the Chinese studies may not be representative of UK patients because of possible differences in the anticancer and COVID-19 therapies patients receive and the types of cancers in the Chinese population. The panel also noted uncertainties in sample overlap between studies and the wide confidence intervals.

The panel discussed the data reported in the QCOVID study (Clift et al. 2020). They commented on the large size of the overall derivation cohort but considered that the sample size for deaths was not particularly large. The panel noted that it was uncertain whether the increased risks of hospital admission and mortality in the Clift study are due to immunosuppression from chemotherapy or other potential confounders. The panel also commented that it was not clear, for example, whether patients had received both chemotherapy and radiotherapy and whether there was any difference in risk based on whether anticancer treatment was received recently (that is, within 4 weeks) or less recently.

The panel concluded that the evidence did not support a recommendation that stated to be aware that patients with COVID-19 are at risk of severe disease following systemic anticancer treatment. However, they agreed that the uncertainty in the current evidence base should be reflected in the revised recommendation. To address the uncertainty in the evidence base, as noted by the panel, the following research recommendations for NG161 (based on the review question for this guideline update) are proposed:

Research recommendation 1

Are patients with cancer and COVID-19 who are receiving/have recently received systemic anticancer treatment (SACT) (i.e. within the 4 weeks preceding a diagnosis of COVID-19) at increased risk of severe COVID-19 illness or death?

Population: All patients diagnosed with cancer and laboratory confirmed COVID-19
Exposure: Patients with cancer who have received SACT within the 4 weeks preceding a diagnosis of COVID-19

Comparator: Patients with cancer who have not received SACT within the 4 weeks preceding a diagnosis of COVID-19

Outcomes: All-cause mortality, COVID-19 related mortality, cancer-related mortality, severe COVID-19 illness measures (note these include mechanical ventilation and ICU stay, and may be reported as composite outcomes), quality of life, length of hospital stay.

All-cause mortality, COVID-19-related mortality and cancer-related mortality are critical outcomes.

It is recommended that this research should also consider:

- if there are specific types of SACT carrying increased risk of poor outcomes from COVID-19
- if there are specific types of cancer for which SACT may carry increased risk of poor outcomes from COVID-19
- if there is a difference in any risk of poor outcomes from COVID-19 between people who have received SACT alone, radiotherapy alone, or both SACT and radiotherapy
- if there is a difference in any risk of poor outcomes from COVID-19 between children and young people who have received SACT and adults who have received SACT

Research recommendation 2

Are people who have had SACT recently (i.e. within the 4 weeks preceding a diagnosis of COVID-19) at increased risk of poor outcomes from COVID-19 compared with those who had SACT less recently?

Population: All patients diagnosed with cancer and laboratory confirmed COVID-19 receiving SACT
Exposure: Patients with cancer who have received SACT within the 4 weeks preceding a diagnosis of COVID-19

Comparator: Patients with cancer who have received SACT more than 4 weeks preceding a diagnosis of COVID-19

Outcomes: All-cause mortality, COVID-19 related mortality, cancer-related mortality, severe COVID-19 illness measures (note these include mechanical ventilation and ICU stay, and may be reported as composite outcomes), quality of life, length of hospital stay.

All-cause mortality, COVID-19-related mortality and cancer-related mortality are critical outcomes.

Trade-off between benefits and harms

The panel considered the trade-off between benefits and harms for people with cancer. They emphasised the importance of avoiding undertreatment of cancer during the pandemic and concluded that, for most people with cancer, the benefits of receiving SACT outweighed the risks from COVID-19. However, the panel felt that it would be important for a clinician to fully discuss the risks and benefits with the individual patient and reach a shared decision, highlighting that the risks of SACT adversely affecting risk of COVID-19 and an increased risk of COVID-19 severity could not be ruled out. Based on their expert opinion, observations in practice and the evidence, the panel emphasised the importance of considering other factors beyond SACT that might predispose to an increased risk from COVID-19, such as age, sex, comorbidities, diagnosis of haematological malignancy, and severity of cancer. The panel also noted the importance of clinicians discussing with patients the risks of delaying anticancer treatment and the risk of cancer progression.

The panel discussed the trade-off between benefits and harms for the health and care system. They noted that different services and local areas were likely to have different COVID-19 prevalence rates and ways of adapting services to provide safe

care. They felt it was important to highlight that services should only provide care when safe and practical to do so, which may vary regionally, and nationally if different infection rates or bed pressures occur. Thus, it would be important for local areas to consider if they could treat cancer patients with COVID-19, balancing the risks to the patient of delaying treatment against the risks to the service, healthcare workers, and other patients without COVID-19. The panel agreed that it was important to retain recommendations in NG161 around service capacity in the event of future local outbreaks or subsequent waves of COVID-19.

Implementation and resource considerations

There is no formal economic evaluation for the rapid COVID guidelines. There may be local spikes in infections that change local services and their ability to deliver SACT, but this is also likely to impact on individual patient risks and benefits for SACT.

The panel also acknowledged that the NHS England interim treatment changes during the COVID-19 pandemic provided treatment options for patients with the aim of reducing need for services because of adverse events, such as neutropenia, and reducing risks of infection and subsequent complications.

Other considerations

The panel noted that the evidence review did not capture evidence on patient experience. Patient quality of life was within the review protocol, but no included studies reported this outcome. The panel did, however, consider the views of the patient representative on the panel. The patient representative stressed the importance of access to good cancer care and highlighted that deferring cancer treatments may have a significant impact on a patient's mental wellbeing and on those who support and care for them.

The panel highlighted that the low levels of intensive therapy unit (ITU) utilisation in the UK cohort (Lee et al. 2020a) could have been due to provision of intensive care outside of specialist units, triaging of cancer patients and judgements made on ceiling of care at peak times in the pandemic, rather than a lack of ITU beds. As such, the panel did not consider this to necessarily indicate a great disparity between

the UK and other countries included in the evidence base. Furthermore, in the panel's experience people who were likely to benefit from intensive care treatment had received it.

There was a lack of evidence for children with cancer and COVID-19 in the included studies. A research recommendation has been added to consider this area. The panel noted that the prevailing evidence (not included in this evidence review) currently indicates that mortality is low in children.

The panel noted that the UK cohort study (Lee et al. 2020a, Lee et al. 2020b) did not provide information on ethnicity, which is now understood to be an important risk factor for COVID-19 severity. However, the committee did consider that people of certain ethnicity, such as black and Asian, were now known to be at higher risk of severe COVID-19 and felt it important to include this in the revised recommendations.

COVID-19 rapid guideline: delivery of radiotherapy (NG162)

Relative value of different outcomes

When developing the review protocol, the expert panel identified all-cause mortality, COVID-19-related mortality and cancer-related mortality as critical outcomes. The panel discussed these outcomes and agreed that all-cause mortality was likely to be the most critical and reliable outcome, as assigning mortality to COVID-19 or cancer may be less reliable.

The panel discussed the GRADE profile for all-cause mortality with radiotherapy and agreed that there was, on balance, no difference. They noted the uncertainty in the available evidence and did not feel it was possible to rule out that radiotherapy did have some impact on COVID-19 severity or mortality. However, coupled with their experience and understanding of the COVID-19 pandemic, the panel discussed that the evidence suggested that COVID-19 severity was likely to be mostly driven by the patient's age, sex, comorbidities and stage of cancer.

The panel also discussed the cancer-specific hazard ratios in the QCOVID study (Clift et al. 2020) showing increased risks of hospital admission and mortality from

COVID-19 for people who had received radiotherapy in the past 6 months. They noted some areas of uncertainty in the data.

The panel did not feel it was possible to make definitive conclusions for subgroups of cancer type or specific types or locations of radiotherapy based on current evidence. However, they did note that some types of radiotherapy were more likely to affect lung function. As such, they felt it important that clinicians consider the risks and benefits for each individual patient and do that in a collaborative way through discussions with the patient.

On balance, the panel did not think the current evidence warranted a change to NG162 guideline recommendations. Current guideline recommendations do not suggest that COVID-19 alone is a reason to withhold radiotherapy. The new evidence supports the recommendations and is not sufficient to add further clarity on when radiotherapy should be withheld or given.

Quality of the evidence

The certainty of the evidence base was low as rated by GRADE. The panel also noted the lack of data available for radiotherapy and small sample sizes in the studies included in the evidence review. There were also issues of missing data or lack of detail, uncertainty in potential confounding factors (such as whether patients receiving radiotherapy were different from those not receiving radiotherapy), and whether there are specific cancers or types of radiotherapy that impact on COVID-19 severity. The panel also noted uncertainties in patient overlap between Chinese studies and the wide confidence intervals.

The panel felt that the 2 largest studies (Lee et al, 2020a and Kuderer et al. 2020) were the most applicable to the UK. However, the numbers receiving radiotherapy in the studies were too small to provide any certainty in the evidence for radiotherapy, particularly as there were likely to be a broad spectrum of radiotherapy types and locations included.

The panel considered that the Chinese studies may not be representative of UK patients due to possible differences in the anticancer and COVID-19 therapies patients received and the types of cancers in the Chinese population.

The panel noted that the data in the QCOVID study (Clift et al. 2020) showed increased risks of hospital admission and mortality due to COVID-19 in people who had received radiotherapy in the previous 6 months. However, the panel considered that there was uncertainty associated with these data (including types of radiotherapy administered, whether risks differed depending on how recently radiotherapy had been received and whether there was any overlap in data for people who had received chemotherapy and radiotherapy).

On balance the panel felt that the evidence was too limited to change current recommendations.

To address the uncertainty in the evidence base, as noted by the panel, the following research recommendations are proposed:

Research recommendation 1

Are patients with cancer and COVID-19 who are receiving/have recently received radiotherapy (i.e. within the 4 weeks preceding a diagnosis of COVID-19) at increased risk of severe COVID-19 illness or death?

Population: All patients diagnosed with cancer and laboratory confirmed COVID-19
Exposure: Patients with cancer who have received radiotherapy within the 4 weeks preceding a diagnosis of COVID-19

Comparator: Patients with cancer who have not received radiotherapy within the 4 weeks preceding a diagnosis of COVID-19

Outcomes: All-cause mortality, COVID-19 related mortality, cancer-related mortality, severe COVID-19 illness measures (note these include mechanical ventilation and ICU stay, and may be reported as composite outcomes), quality of life, length of hospital stay.

All-cause mortality, COVID-19-related mortality and cancer-related mortality are critical outcomes.

It is recommended that this research should also consider:

- if there are specific types of radiotherapy carrying increased risk of poor outcomes from COVID-19
- if there are specific types of cancer for which radiotherapy may carry increased risk of poor outcomes from COVID-19
- if there is a difference in any risk of poor outcomes from COVID-19 between people who have received SACT alone, radiotherapy alone, or both SACT and radiotherapy
- if there is a difference in any risk of poor outcomes from COVID-19 between children and young people who have received radiotherapy and adults who have received radiotherapy

Research recommendation 2

Are people who have had radiotherapy recently (i.e. within the 4 weeks preceding a diagnosis of COVID-19) at increased risk of poor outcomes from COVID-19 compared with those who had radiotherapy less recently?

Population: All patients diagnosed with cancer and laboratory confirmed COVID-19 receiving radiotherapy
Exposure: Patients with cancer who have received radiotherapy within the 4 weeks preceding a diagnosis of COVID-19

Comparator: Patients with cancer who have received radiotherapy more than 4 weeks preceding a diagnosis of COVID-19

Outcomes: All-cause mortality, COVID-19 related mortality, cancer-related mortality, severe COVID-19 illness measures (note these include mechanical ventilation and ICU stay, and may be reported as composite outcomes), quality of life, length of hospital stay.

All-cause mortality, COVID-19-related mortality and cancer-related mortality are critical outcomes.

Trade-off between benefits and harms

The panel considered the trade-off between benefits and harms for people with cancer who may need radiotherapy during the COVID-19 pandemic. They emphasised the importance of avoiding undertreatment of cancer during the pandemic and concluded that for most cancer patients the benefits of receiving radiotherapy outweighed the risks from COVID-19. However, there may be certain types of radiotherapy that represent higher risk of immunosuppression and it would be important for a clinician to weigh each person's risks individually. Based on the panel's opinion, observations in practice and the evidence, they expressed the importance for consideration of other factors beyond radiotherapy that might predispose the patient to an increased risk from COVID-19, such as age, sex, comorbidities, and severity of cancer.

The panel discussed the trade-off between benefits and harms for service delivery. They noted that different services and local areas were likely to have different COVID-19 incidence rates and ways of adapting services to provide safe care. They felt it was important to highlight that services should only provide care when safe and practical to do so, which may vary regionally and nationally if different infection rates or bed pressures occur. Thus, it would be important for local areas to consider if they could treat cancer patients with COVID-19, balancing the risks to the patient of delaying treatment against the risks to the service, healthcare workers, and other patients. They noted that it was important to retain recommendations around service capacity in the event of future local outbreaks or subsequent waves of COVID-19.

Overall, the panel did not feel that the evidence was sufficient to change current recommendations. They noted that the recommendations are likely to still be valid in the coming months, as the recommendations do not mandate against radiotherapy, but highlight the importance of assessing the risks and benefits for the patient and service and suggest ways to prioritise if needed.

Implementation and resource considerations

There is no formal economic evaluation for the rapid COVID guidelines. The panel considered that the new evidence does not provide any information on the costs and resources of delivering radiotherapy. However, the panel noted that as radiotherapy services return to normal this should not incur additional costs as this would be a return to baseline levels before the COVID-19 pandemic. The panel also considered that costs may reduce if hypofractionated dosing schedules continue after the COVID-19 pandemic.

Other considerations

The panel noted that evidence on the impact of giving radiotherapy to patients with COVID-19 was limited.

The panel observed that there is a need for the current guideline recommendations in the event of subsequent spikes of COVID-19 nationally or locally. It was not felt necessary to be more prescriptive in the recommendations because what is safe and practical in one hospital may not be in another.

The panel were aware that due to the COVID-19 pandemic, alternative radiotherapy regimens were being used in practice, which may minimise exposure to and risk of COVID-19. The panel discussed if radiotherapy-associated lymphopenia could contribute to severity of infection or risk of new COVID-19. The current evidence base was not sufficient to address this issue, therefore the panel made the following additional research recommendation:

Research recommendation 3

Does radiation-induced lymphopenia predispose patients to an increased risk of new COVID-19 and does it contribute to patients developing more severe COVID-19?

Population: Patients with cancer receiving radiotherapy

Exposure: Patients with cancer who have received radiotherapy and have developed lymphopenia

Comparator: Patients with cancer who have received radiotherapy and have not developed lymphopenia

Outcomes: incidence of new COVID-19, all-cause mortality, COVID-related mortality, cancer-related mortality, measures of severe COVID-19

The panel noted that the evidence review did not capture evidence on patient experience. Patient quality of life was within the review protocol, but no included studies reported this outcome. The panel did, however, consider the views of the patient representative on the panel. The patient representative stressed the importance of access to good cancer care and highlighted that deferring cancer treatments may have a significant impact on a patient's mental wellbeing and on those who support and care for them.

The panel highlighted that the low levels of intensive therapy unit (ITU) utilisation in the UK cohort (Lee et al. 2020) could have been due to provision of intensive care outside of specialist units, triaging of cancer patients and judgements made on ceiling of care at peak times in the pandemic, rather than a lack of ITU beds per se. As such, the panel did not consider this to necessarily indicate a great disparity between the UK and other countries included in the evidence base. Furthermore, in the panel's experience people who were likely to benefit from intensive care treatment had received it.

There was a lack of evidence for children in the included studies. A research recommendation has been added in this area. The panel noted that the prevailing evidence (not included in this evidence review) currently indicates that mortality is low in children. The panel did acknowledge that the travel restrictions had impacted on children's access to proton beam therapy, but this is outside the scope of the guideline.

The panel noted that the UK cohort study (Lee et al. 2020) did not provide information on ethnicity, which is now understood to be an important risk factor for COVID-19 severity.

References

Kuderer NM, Choueiri TK, Shah DP et al. (2020) Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 395(10241): 1907–18

Lee YW, Cazier JB, Starkey T et al. (2020a) COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. The Lancet 395(10241): 1919–26

Lee YW, Cazier JB, Starkey T et al. (2020b) COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncology 21: 1309–16

Liang W, Guan, Chen R et al. (2020) Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncology 21(3): 335–7

Oh WK (2020) COVID-19 infection in cancer patients: early observations and unanswered questions. Lancet Oncology 31(7): 838–9

Poortmans PM, Guarnei V, Cardoso MJ (2020) Cancer and COVID-19: what do we really know? Lancet 395(10241): 1884–85

Tian J, Yuan X, Xiao J et al. (2020) Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncology 21(7): 893–903

Zhang L, Zhu F, Xie L et al. (2020) Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Annals of Oncology 31(7): 894–901

Supporting references

Clift AK, Coupland CAC, Keogh RH et al. (2020) Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 371

Appendix 1 Protocol for the rapid evidence review

The protocol for the rapid evidence review covered the COVID-19 rapid guidelines on delivery of systemic anticancer treatments (NG161) and delivery of radiotherapy (NG162)

Variable	Details
Review question	Are patients with cancer and COVID-19 who are receiving/have recently received systemic anticancer treatment (SACT) or radiotherapy at increased risk of severe COVID-19 illness or death?
Background/objectives	During guideline development, early Chinese data and unpublished modelling indicated that the cancer therapies that cancer patients received may cause poorer outcomes with COVID-19, likely due to immunosuppression. The aim of this review is to determine if the evidence base has changed and if we have more conclusive evidence that cancer therapies are associated with risk of COVID-19 mortality and severity of disease.
Original review questions (if relevant)	What is the level of risk of COVID-19 (and mortality in particular) specifically in patients receiving systemic anticancer treatment (chemotherapy)?
Type of review question	Prognosis
Language	Only publications available in full text in English will be included
Study design	Prospective cohort studies Retrospective cohort studies Case-control studies Systematic reviews of above
Status	Published papers (full text only) and preprints
Population	All patients diagnosed with cancer and laboratory confirmed COVID-19. Subgroups: SACT: • Chemotherapy • Immunotherapy • Targeted therapy (includes antibodies and small molecules) • Radiotherapy Exclusions: Proton beam therapy (as not within original scope of NG161) Surgery (not within scope)

Variable	Details
	Additional considerations: Where evidence is available and sample sizes are sufficient to allow conclusions to be drawn, we will explore specific cancer regimens, types of tumour, and stage of disease. Hormone therapy is generally not considered SACT in the UK, but if deemed clinically relevant by the expert panel we may consider this. If feasible in the timeframe and clinically needed by the expert panel, we will look at studies including suspected COVID-19 patients
Exposure	Patients with cancer who have received systemic anticancer therapy or radiotherapy within 4 weeks before COVID-19 diagnosis
Comparator	Patients with cancer and COVID-19 diagnosis who have not received any SACT or radiotherapy within 4 weeks of COVID-19 diagnosis
Outcomes	All-cause mortality COVID-19 related mortality Cancer-related mortality Severe COVID-19 illness measures (note these include mechanical ventilation and ICU stay, and may be reported as composite outcomes) Quality of life Length of hospital stay. All-cause mortality, COVID-19-related mortality and cancer-related mortality are critical outcomes.
Other criteria for inclusion / exclusion of studies	Exclusions: Narrative reviews, non-comparative studies, case series, case reports, letters, editorials, commentaries Studies not taking into account age as a confounding factor at analysis.
Review strategies	A list of studies excluded at full text with reason(s) for exclusion will be provided. Depending on the volume of evidence available we may prioritise study inclusion based on study design. Data on all included studies will be extracted into brief evidence tables and risk of bias will be assessed.

Appendix 2 Focused search strategy

Review question: Are patients with cancer and COVID-19 who are receiving/have recently received systemic anticancer treatment (SACT) or radiotherapy at increased risk of severe COVID-19 illness or death?

Search strategy for the review question

Database	Platform	Segment searched
MEDLINE ALL	Ovid	1946 to July 02, 2020
Embase	Ovid	1974 to 2020 July 02
Cochrane Library	Wiley	Issue 7 of 12, July 2020
Pre-prints – bioRxiv and medRxiv	RIS via EPPI	RIS file received on 2020-07-06
WHO COVID-19 database	WHO website	Searched 2020-07-06

Database strategies

Strategies for MEDLINE and WHO presented below, full details available on request.

MEDLINE ALL

1 exp coronavirus/ (19313)
2 exp Coronavirus Infections/ (19081)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1362)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (27957)
5 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (28509)
6 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (276)
7 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (69)
8 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (445)
9 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (256)

10 "severe acute respiratory syndrome*".ti,ab,kw,kf. (7759)
11 or/1-10 (51106)
12 limit 11 to yr="2019 -Current" (31664)
13 Drug Therapy/ (30519)
14 exp Drug Therapy, Combination/ (323756)
15 exp Antineoplastic Protocols/ (140124)
16 exp Antineoplastic Agents/ (1095638)
17 Chemotherapy, Adjuvant/ (40523)
18 (chemotherap* or antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw. (431357)
19 ((anticancer* or anti-cancer* or antitumo?r* or anti-tumo?r* or anticarcinogen* or anticarcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw. (107745)
20 exp Chemoradiotherapy/ (14550)
21 (chemoradiotherap* or radiochemotherap* or chemoradiation*).tw. (30223)
22 (chemo adj1 (radiotherap* or radiation)).tw. (3854)
23 Combined Modality Therapy/ (174236)
24 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (4788)
25 ((tri-modal* or trimodal* or multi-modal* or multimodal*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw. (18983)
26 TMT.tw. (3229)
27 or/13-26 (1690437)
28 exp Radiotherapy/ (184984)
29 Radiation Oncology/ (4116)
30 radiotherapy.fs. (190853)
31 (radiotherap* or radiotreat* or roentgentherap* or radiosurg*).tw. (179308)
32 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw. (244481)
33 (RT or RTx or XRT).tw. (201207)
34 Stereotaxic Techniques/ (15135)
35 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw. (9490)
36 (SABR or SBRT or SRS).tw. (13853)
37 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw. (1730)
38 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw. (10232)
39 or/28-38 (664008)
40 27 or 39 (2170908)
41 12 and 40 (1334)
42 (MEDLINE or pubmed).tw. (206287)
43 systematic review.tw. (157246)
44 systematic review.pt. (130416)
45 meta-analysis.pt. (116701)
46 intervention$.ti. (148969)
47 or/42-46 (461719)

48 Observational Studies as Topic/ (5127)
49 Observational Study/ (81322)
50 Epidemiologic Studies/ (8347)
51 exp Case-Control Studies/ (1087760)
52 exp Cohort Studies/ (2006522)
53 Cross-Sectional Studies/ (331033)
54 Controlled Before-After Studies/ (525)
55 Historically Controlled Study/ (184)
56 Interrupted Time Series Analysis/ (900)
57 Comparative Study.pt. (1865036)
58 case control$.tw. (128824)
59 case series.tw. (74254)
60 (cohort adj (study or studies)).tw. (206054)
61 cohort analy$.tw. (8043)
62 (follow up adj (study or studies)).tw. (49211)
63 (observational adj (study or studies)).tw. (106827)
64 longitudinal.tw. (244864)
65 prospective.tw. (569419)
66 retrospective.tw. (530553)
67 cross sectional.tw. (352713)
68 or/48-67 (4656576)
69 47 or 68 (4997704)
70 41 and 69 (266)
71 limit 70 to english language (256)
72 limit 71 to (letter or historical article or comment or editorial or news) (15)
73 71 not 72 (241).

World Health Organization COVID-19 database

Variable	Details
Name	World Health Organization Global research on coronavirus disease (COVID-19)
URL	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
Notes	"WHO is gathering the latest scientific findings and knowledge on coronavirus disease (COVID-19) and compiling it in a database. We update the database daily from searches of bibliographic databases, hand searches of the table of contents of relevant journals, and the addition of other relevant scientific articles that come to our attention."
Search terms	tw:((chemotherap* OR antineoplastic* OR anti-neoplastic* OR polychemotherap* OR anticancer* OR anti-cancer* OR antitumor* OR anti-tumor* OR antitumour* OR anti-tumour* OR anticarcinogen* OR anticarcinogen* OR chemoradiotherap* OR radiochemotherap* OR chemoradiation* OR radiotherap* OR radiation OR radiotreat* OR roentgentherap* OR radiosurg* OR irradiat* OR roentgen OR x-ray OR xray OR "combin* modalit*" OR tri-modal* OR trimodal* OR multi-modal* OR multimodal* OR stereotac* OR stereotax* OR hypofraction* OR hyperfraction* OR tmt OR rt OR rtx OR xrt OR sabr OR sbrt OR srs OR hfsrt OR cahrt OR chartwel OR imrt OR ahrt OR a-hypo OR hypotrt)) AND (tw:(case-control* OR "case control" OR "clinical control" OR "systematic review*" OR cohort* OR "family stud*" OR meta-analysis OR "meta analysis" OR longitud* OR "retrospectiv* stud*" OR "comparativ* stud*" OR "prospectiv* stud*" OR "follow up" OR observational* OR "epidemiologic* stud*" OR "cross sectional" OR "case series" OR case-series OR "case report*" OR case-report*)) **Filters applied** –English language
How the results were selected	All filtered selected
Results	184

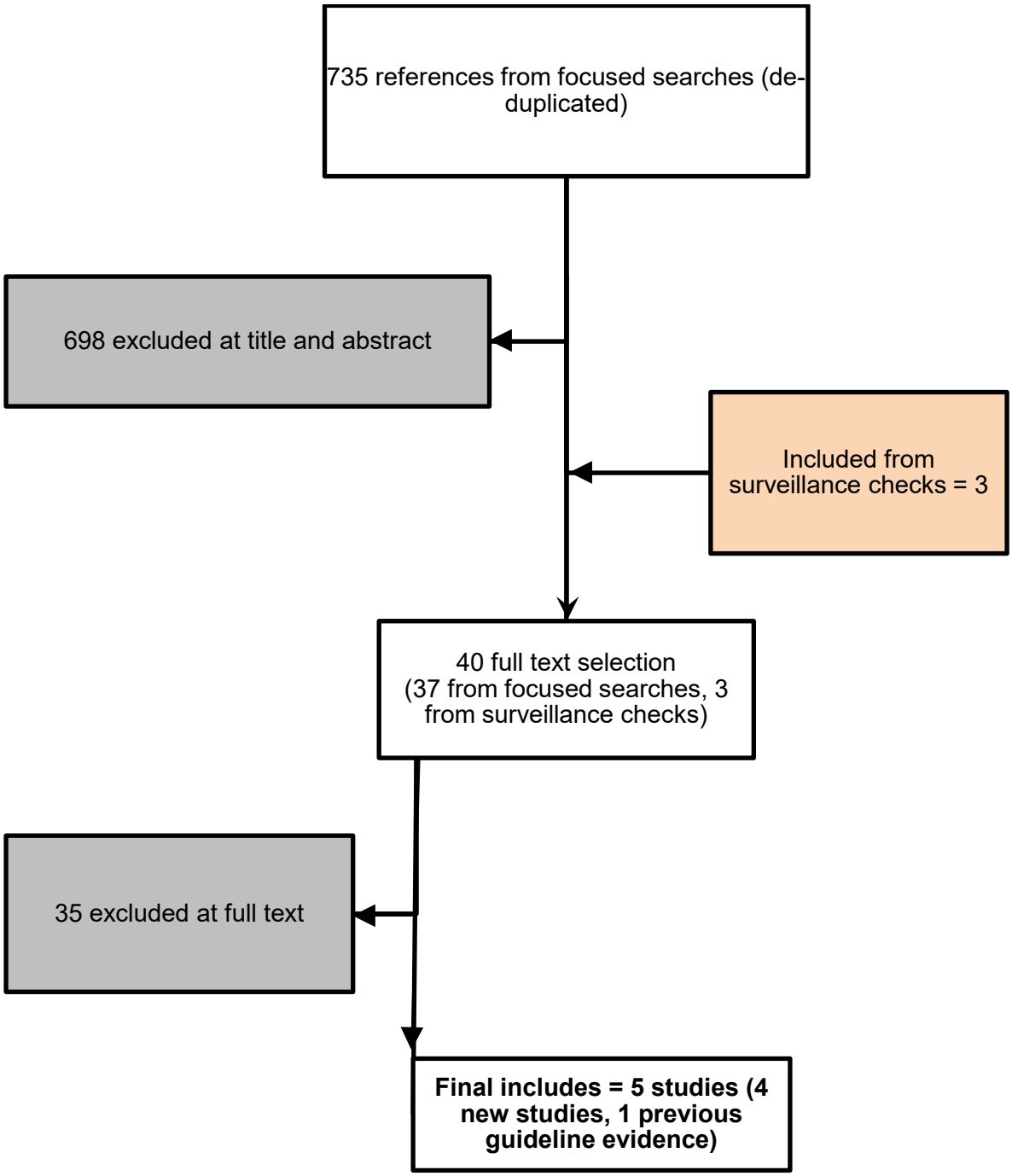
A range of sources were also searched in surveillance checks to identify additional published evidence. These sources included:

- BMJ Best Practice Coronavirus disease 2019 (COVID-19)
- Ovid MEDLINE ® ALL
- Ovid Embase
- bioRxiv and medRxiv pre-prints
- NICE Evidence Search (this includes guidance from Royal Colleges and other professional bodies on COVID-19)
- TRIP database
- Centre for Evidence-based medicine (CEBM) COVID-19 Evidence Service
- Centers for Disease Control and Prevention (CDC) [US]

- Cochrane Rapid Reviews on COVID-19
- ECRI COVID-19 Resource Center
- Epistemonikos
- European Centre for Disease Prevention and Control
- MHRA
- Resources from Royal Colleges and other professional bodies on COVID-19 which are not covered by NICE Evidence Search
- World Health Organization Country & Technical Guidance - Coronavirus disease (COVID-19)
- CDSR and CENTRAL in the Cochrane Library

Appendix 3 Evidence selection

Study flow diagram to completion of draft evidence review (13 July 2020) for expert panel meeting 1



NB: Following completion of the draft evidence review (13 July 2020) for the first meeting of the expert panel, we considered studies identified in surveillance checks (until 24 September 2020) to identify any additional new evidence. An additional 24 search records were

identified, of which 22 were examined at full text stage by 2 reviewers. One relevant item was identified: an additional report (Lee et al. 2020b) of an already included study (Lee et al. 2020a). This was added to the evidence review. The remaining search records were excluded. See below for a table of studies excluded at full text during these surveillance checks.

List of studies excluded at full text to completion of review (13 July 2020) for expert panel meeting 1

Study	Reason for exclusion
Abdelfattah, NM and Sabri, NA (2020) Chemotherapy and COVID19; Administration of Chemotherapy at Home. Ann Hematol Oncol Res 1(1): 1006	- Not a study design specified in protocol
Assaad, Souad, Avrillon, Virginie, Fournier, Marie-Line et al. (2020) High mortality rate in cancer patients with symptoms of COVID-19 with or without detectable SARS-COV-2 on RT-PCR. European journal of cancer (Oxford, England : 1990)	- Age not controlled for in study design as a known confounder
Bogani, Giorgio, Ditto, Antonino, Bosio, Sara et al. (2020) Cancer patients affected by COVID-19: Experience from Milan, Lombardy. Gynecologic oncology	- Not a study design specified in protocol
Buckstein, Michael, Skubish, Samantha, Smith, Kimberly et al. (2020) Experiencing the Surge: Report from a Large New York Radiation Oncology Department During the COVID-19 Pandemic. Advances in radiation oncology	- Outcomes do not match those specified in the protocol
Cao Maria, Gonzalez-Cao, Basa Monica, Antonazas-Basa, Puertolas, Teresa et al. Cancer immunotherapy does not increase the risk of death by COVID-19 in melanoma patients. medrxiv preprint	- Population - not laboratory confirmed COVID-19 - Age not controlled for in study design as a known confounder
Dai, Mengyuan, Liu, Dianbo, Liu, Miao et al. (2020) Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer discovery 10(6): 783-791	- Age not controlled for in study design as a known confounder - Cancer therapy not received within past 4 weeks or unclear
Desai, Aakash, Sachdeva, Sonali, Parekh, Tarang et al. (2020) COVID-19 and cancer: lessons from a pooled meta-analysis. JCO global oncology 6	- Not a study design specified in protocol
Garassino, Marina Chiara, Whisenant, Jennifer G, Huang, Li-Ching et al. (2020) COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. The Lancet. Oncology	- Cancer therapy not received within past 4 weeks or unclear - Age not controlled for in study design as a known confounder
Hrusak, Ondrej, Kalina, Tomas, Wolf, Joshua et al. (2020) Flash survey on SARS-CoV-2	- Not a study design specified in protocol

Study	Reason for exclusion
infections in pediatric patients on anti-cancer treatment. European Journal of Cancer	
Joharatnam-Hogan, Nalinie, Hochhauser, Daniel, Shiu, Kai-Keen et al. (2020) Outcomes of the 2019 Novel Coronavirus in patients with or without a history of cancer-a multi-centre North London experience. medRxiv	- Exposure and/or comparison do not match protocol
Lai Alvina, G, Pasea, Laura, Banerjee, Amitava et al. Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency. medrxiv preprint	- Not a study design specified in protocol - Exposure and/or comparison do not match protocol
Lee Karla, A, Ma, Weinjie, Sikavi Daniel, R et al. Cancer and risk of COVID-19 through a general community survey. medrxiv preprint	- Cancer therapy not received within past 4 weeks or unclear
Magleby, Reed, Westblade, Lars F, Trzebucki, Alex et al. (2020) Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients with Coronavirus Disease 2019. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	- Outcomes do not match those specified in the protocol
Moujaess, Elissar; Kourie, Hampig Raphael; Ghosn, Marwan (2020) Cancer patients and research during COVID-19 pandemic: A systematic review of current evidence. Critical reviews in oncology/hematology 150: 102972	- Not a study design specified in protocol
Namal, Esat, Dinc, Nur, Saglam, Sezer et al. (2020) Management of oncology patients receiving anti-cancer treatment in the COVID-19 pandemic	- Age not controlled for in study design as a known confounder - Exposure and/or comparison do not match protocol Outcomes do not match those specified in the protocol
Ning, Matthew S, McAleer, Mary Frances, Jeter, Melenda D et al. (2020) Mitigating the impact of COVID-19 on oncology: Clinical and operational lessons from a prospective radiation oncology cohort tested for COVID-19. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 148: 252-257	- Age not controlled for in study design as a known confounder - Cancer therapy not received within past 4 weeks or unclear - Exposure and/or comparison do not match protocol
Núñez-Torrón, Claudia, García-Gutiérrez, Valentín, Tenorio-Núñez, María Concepción et al. (2020) Poor outcome in patients with acute leukemia on intensive chemotherapy and COVID-19. Bone Marrow Transplantation: 1-3	- Age not controlled for in study design as a known confounder - Not a study design specified in protocol

Study	Reason for exclusion
Robilotti Elizabeth, V., Babady N., Esther, Mead Peter, A. et al. Determinants of Severity in Cancer Patients with COVID-19 Illness. medrxiv preprint	- Duplicate reference
Robilotti, Elizabeth V, Babady, N Esther, Mead, Peter A et al. (2020) Determinants of COVID-19 disease severity in patients with cancer. Nat. med	- Age not controlled for in study design as a known confounder
Russell, Beth, Moss, Charlotte, George, Gincy et al. (2020) Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience 14: 1022	- Population - not laboratory confirmed COVID-19 - Exposure and/or comparison do not match protocol
Sharma, Akanksha, Malviya, Rishabha, Kumar, Vinod et al. (2020) Severity and risk of COVID-19 in cancer patients: An evidence based learning. Dermatologic Therapy: e13778	- Not a study design specified in protocol
Sun, L, Xu, Y, Zhang, T et al. (2020) Impact of the COVID-19 outbreak on adjuvant chemotherapy for patients with stage II or III colon cancer: experiences from a multicentre clinical trial in China. Current Oncology 27(3)	- Not a study design specified in protocol - Population - not laboratory confirmed COVID-19
Vuagnat, Perrine, Frelaut, Maxime, Ramtohul, Toulsie et al. (2020) COVID-19 in breast cancer patients: a cohort at the Institut Curie hospitals in the Paris area. Breast cancer research : BCR 22(1): 55	- Population - not laboratory confirmed COVID-19 - Exposure and/or comparison do not match protocol
Wang, Jie, Song, Qibin, Chen, Yuan et al. Systematic investigations of COVID-19 in 283 cancer patients. medrxiv preprint	- Cancer therapy not received within past 4 weeks or unclear
Wang, T., Liu, S., Joseph, T. et al. (2020) Managing bladder cancer care during the COVID-19 pandemic using a team-based approach. Journal of Clinical Medicine 9(5): 1574	- Not a study design specified in protocol - Exposure and/or comparison do not match protocol
Williams, Matt, Mi, Ella, Calvez Kerlann, Le et al. Estimating the Risks from COVID-19 Infection in Adult Chemotherapy Patients. medrxiv preprint	- Not a study design specified in protocol
Xie, Conghua, Wang, Xiaoyong, Liu, Hui et al. Infection Control of 2019 Novel Corona Virus Disease (COVID-19) in Cancer Patients undergoing Radiotherapy in Wuhan. medrxiv preprint	- Population - not laboratory confirmed COVID-19 - Exposure and/or comparison do not match protocol

Study	Reason for exclusion
Yang Y, Shen C, Hu C (2020) Effect of COVID-19 Epidemic on Delay of Diagnosis and Treatment Path for Patients with Nasopharyngeal Carcinoma. Cancer management and research 12: 3859-3864	- Population - not laboratory confirmed COVID-19 - Exposure and/or comparison do not match protocol
Yang, Kunyu, Sheng, Yuhan, Huang, Chaolin et al. (2020) Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. The Lancet. Oncology	- Age not controlled for in study design as a known confounder
Yu, Jing, Ouyang, Wen, Chua Melvin, L.K. et al. SARS-CoV-2 transmission in cancer patients of a tertiary hospital in Wuhan. medrxiv preprint	- Population - not laboratory confirmed COVID-19 - Age not controlled for in study design as a known confounder - Exposure and/or comparison do not match protocol
Zhang, Hong-Yan, Wang, Lin-Wei, Chen, Yuan-Yuan et al. A Multicentre Study of 2019 Novel Coronavirus Disease Outcomes of Cancer Patients in Wuhan, China. medrxiv preprint	- Age not controlled for in study design as a known confounder
Zhang, Hongyan, Wang, Linwei, Chen, Yuanyuan et al. (2020) Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. Cancer	- Age not controlled for in study design as a known confounder
Indini, Alice, Rijavec, Erika, Ghidini, Michele et al. (2020) Developing a risk assessment score for patients with cancer during the coronavirus disease 2019 pandemic. European journal of cancer (Oxford, England : 1990) 135: 47-50	- Not a study design specified in protocol
Venkatesulu Bhanu, Prasad, Chandrasekar Viveksandeep, Thoguluva, Giridhar, Prashanth et al. A systematic review and meta-analysis of cancer patients affected by a novel coronavirus. medrxiv preprint	- Not a study design specified in protocol - Cancer therapy not received within the past 4 weeks or unclear - Age not controlled for in study design as a known confounder
Yarza, Ram?n, Bover, Mateo, Paredes, Diana et al. (2020) Sars-CoV-2 infection in cancer patients undergoing active treatment. Analysis of clinical features and predictive factors for severe respiratory failure and death. European Journal of Cancer	- Not a study design specified in protocol

List of studies excluded at full text during surveillance checks (13 July 2020 to 24 September 2020)

Study	Reason for exclusion
Maringe, Camille et al. (2020) The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. The Lancet Oncology	- Exposure and/or comparison do not match protocol - Age not controlled for in study design or unclear - Cancer therapy not received within the past 4 weeks or unclear
Angelis, Vasileios, Tippu, Zayd, Joshi, Kroopa et al. (2020) Defining the true impact of coronavirus disease 2019 in the at-risk population of patients with cancer. European journal of cancer (Oxford, England : 1990) 136: 99-106	- Exposure and/or comparison do not match protocol - Age not controlled for in study design or unclear - Cancer therapy not received within the past 4 weeks or unclear
Aznab, Mozaffar (2020) Evaluation of COVID 19 infection in 279 cancer patients treated during a 90-day period in 2020 pandemic. International journal of clinical oncology	- Not a study design specified in protocol *case series* - Age not controlled for in study design or unclear
Bersanelli, Melissa, Zielli, Teresa, Perrone, Fabiana et al. (2020) Clinical impact of COVID-19 in a single-center cohort of a prospective study in cancer patients receiving immunotherapy. Immunotherapy	- Age not controlled for in study design or unclear - Exposure and/or comparison do not match protocol
Chakraborty, Mainak and Pandey, Manoj (2020) Caring for cancer patients in the Covid pandemic: choosing between the devil and deep sea. World journal of surgical oncology 18(1): 220	- Not a study design specified in protocol *Review (not systematic)*
Engelhardt, Monika, Shoumariyeh, Khalid, Rosner, Amelie et al. (2020) Clinical characteristics and outcome of multiple myeloma patients with concomitant COVID-19 at Comprehensive Cancer Centers in Germany. Haematologica	- Cancer therapy not received within the past 4 weeks or unclear - Age not controlled for in study design or unclear
Fillmore Nathanael, R, La, Jennifer, Szalat Raphael, E et al. Prevalence and outcome of Covid-19 infection in cancer patients: a national VA study. medrxiv preprint	- Cancer therapy not received within the past 4 weeks or unclear - Age not controlled for in study design or unclear

Study	Reason for exclusion
Fox, T A, Troy-Barnes, E, Kirkwood, A A et al. (2020) Clinical outcomes and risk factors for severe COVID-19 infection in patients with haematological disorders receiving chemo- or immunotherapy. British journal of haematology	- Age not controlled for in study design or unclear
Jee, Justin, Foote, Michael B, Lumish, Melissa et al. (2020) Chemotherapy and COVID-19 Outcomes in Patients With Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology: jco2001307	- Cancer therapy not received within the past 4 weeks or unclear
Jee, Justin, Stonestrom Aaron, J, Devlin, Sean et al. Oncologic Immunomodulatory Agents in Patients with Cancer and COVID-19. medrxiv preprint	- Cancer therapy not received within the past 4 weeks or unclear - Age not controlled for in study design or unclear
Li, Qiubai, Chen, Lei, Li, Qin et al. (2020) Cancer increases risk of in hospital death from COVID-19 in persons <65 years and those not in complete remission. Leukemia	- Exposure and/or comparison do not match protocol - Age not controlled for in study design or unclear
Liontos, M., Kaparelou, M., Karofylakis, E. et al. (2020) Chemotherapy resumption in ovarian cancer patient diagnosed with COVID-19. Gynecologic Oncology Reports 33: 100615	- Not a study design specified in protocol *case report*
Moss, Charlotte, Dolly, Saoirse, Russell, Beth et al. (2020) One Piece of the Jigsaw for the Cancer Recovery Strategy: Prevalence of COVID-19 in Patients With Cancer. Cancer control : journal of the Moffitt Cancer Center 27(3): 1073274820950844	- Cancer therapy not received within the past 4 weeks or unclear - Age not controlled for in study design or unclear - Exposure and/or comparison do not match protocol - Not a study design specified in protocol
Pala, Laura, Conforti, Fabio, Saponara, Maristella et al. (2020) Data of Italian Cancer Centers from two regions with high incidence of SARS CoV-2 infection provide evidence for the successful management of patients with locally advanced and metastatic melanoma treated with immunotherapy in the era of COVID-19. Seminars in oncology	- Not a study design specified in protocol - Cancer therapy not received within the past 4 weeks or unclear - Age not controlled for in study design or unclear - Exposure and/or comparison do not match protocol
Pinato, D.J., Lee, A.J.X., Biello, F. et al. (2020) Presenting features and early mortality from SARS-CoV-2 infection in cancer patients during	- Cancer therapy not received within the past 4 weeks or unclear

Study	Reason for exclusion
the initial stage of the COVID-19 pandemic in Europe. Cancers 12(7): 1-13	
Qi, Lina, Wang, Kailai, Ye, Chenyang et al. (2020) Special Issues Encountered When Cancer Patients Confront COVID-19. Frontiers in oncology 10: 1380	- Not a study design specified in protocol *Review (not systematic)*
Sanchez-Pina, Jose Maria, Rodriguez Rodriguez, Mario, Castro Quismondo, Nerea et al. (2020) Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies. European journal of haematology	- Age not controlled for in study design or unclear
Shi, Zhuqing, Resurreccion W., Kyle, Wang, Chi-Hsiung et al. Association of Cancer with Risk and Mortality of COVID-19: Results from the UK Biobank. medrxiv preprint	- Exposure and/or comparison do not match protocol
Tian, Yehong, Qiu, Xiaowei, Wang, Chengxiang et al. (2020) Cancer associates with risk and severe events of COVID-19: A systematic review and meta-analysis. International journal of cancer	- Exposure and/or comparison do not match protocol
van Dam, Peter A, Huizing, Manon, Mestach, Gino et al. (2020) SARS-CoV-2 and cancer: Are they really partners in crime?. Cancer treatment reviews 89: 102068	- Not a study design specified in protocol *narrative review*
Walker, Sara, Thomson Maureen, C, Campbell, Frances et al. Keep calm and carry on: safety, feasibility and early outcomes of head and neck cancer treatment during the COVID-19 pandemic. medrxiv preprint	- Exposure and/or comparison do not match protocol - Age not controlled for in study design or unclear

Appendix 4 Evidence tables

New evidence

Lee et al. (2020)

Bibliographic reference/s	**COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study, Lee et al 2020a** **COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study, Lee et al 2020b**
Study name	The UK Coronavirus Cancer Monitoring Project (UKCCMP)
Publication status	Published
Registration	NA
Study type	Cohort (prospective)
Study dates	March 18 2020 to April 26 2020 (Lee et al, 2020a) March 18 2020 to May 8 2020 (Lee et al, 2020b)
Objective	To describe the clinical and demographic characteristics and COVID-19 outcomes in patients with cancer
Country/ Setting	UK
Cohort source	Cancer centres from across UK (n=55 Lee et al, 2020a, n=61 Lee et al, 2020b)
Participant numbers	800 (Lee et al, 202a), 1044 (Lee et al, 2020b)
Population specifics	Laboratory confirmed COVID-19 (RT-PCR assay test from a throat or nose swab was positive for SARS-CoV-2). Patients with active cancer were defined as those with metastatic cancer, or on anticancer treatment in any setting (curative, radical, adjuvant, or neoadjuvant setting) or treated within the past 12 months with surgery cytotoxic chemotherapy, or radiotherapy.
Prognostic factors	Chemotherapy, immunotherapy, hormone therapy, targeted therapy, radiotherapy
Baseline study sample characteristics	Some of the key characteristics from the primary publication (Lee et al, 2020a) are extracted below but please refer to full papers for details of other characteristics, particularly around cancer type and stage.

	All patients (n=800)	Patients who died (n=226)	Patients who survived (n=574)
Male	449 (56%)	146 (65%)	303 (53%)
Median age, years (IQR)	69 (59-76)	73 (66-80)	66 (57-74)
Cardiovascular disease	109 (14%)	48 (21%)	61 (11%)
COPD	61 (8%)	24 (11%)	37 (6%)
Diabetes	131 (16%)	46 (20%)	85 (15%)
Hypertension	247 (31%)	92 (41%)	155 (27%)

<table>
<tr><td>Bibliographic reference/s</td><td>COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study, Lee et al 2020a
COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study, Lee et al 2020b</td></tr>
<tr><td></td><td>
<table>
<tr><td>No comorbidity</td><td>169 (21%)</td><td>27 (12%)</td><td>142 (25%)</td></tr>
<tr><td>Metastatic cancer</td><td>347 (43%)</td><td>103 (46%)</td><td>244 (43%)</td></tr>
<tr><td>Remission</td><td>21 (3%)</td><td>3 (1%)</td><td>18 (3%)</td></tr>
<tr><td>Chemotherapy*</td><td>281 (35%)</td><td>75 (33%)</td><td>206 (36%)</td></tr>
<tr><td>Immunotherapy*</td><td>44 (6%)</td><td>10 (4%)</td><td>34 (6%)</td></tr>
<tr><td>Targeted therapy*</td><td>72 (9%)</td><td>16 (7%)</td><td>56 (10%)</td></tr>
<tr><td>Radiotherapy*</td><td>76 (10%)</td><td>18 (8%)</td><td>58 (10%)</td></tr>
<tr><td>Hormone therapy*</td><td>64 (8%)</td><td>21 (9%)</td><td>43 (7%)</td></tr>
<tr><td>No cancer therapy*</td><td>272 (34%)</td><td>92 (41%)</td><td>180 (31%)</td></tr>
</table>
* Within 4 weeks of COVID-19 diagnosis
</td></tr>
<tr><td>Attrition</td><td>N/A Although note there is missing data, notably 25% missing for cancer stage and 15% missing for comorbidities.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with a radiological or clinical diagnosis of COVID-19, without a positive RT-PCR test were excluded (Lee et al, 2020a, Lee et al, 2020b).
Patients with skin cancer or unspecified tumour subtypes were not included in further analyses (Lee et al, 2020b).</td></tr>
<tr><td>Data collection</td><td>Prospective data collection was performed by the pan-UK cancer centre emergency response network.</td></tr>
<tr><td>Outcome measure</td><td>The primary outcome was all-cause mortality reported during hospital admission.</td></tr>
<tr><td>Follow-up</td><td>Until death or hospital discharge.</td></tr>
<tr><td>Main results</td><td>Odds of death by therapy type based on univariate regression analysis (all patients) (Lee et al, 2020a)
<table>
<tr><td>All-cause mortality</td><td>Odd ratio (95% CI)</td><td>p value</td><td>Adjusted p value</td></tr>
<tr><td>Chemotherapy</td><td>0·78 (0·55 –1·11)</td><td>0·173</td><td>1·000</td></tr>
<tr><td>Immunotherapy</td><td>0.60 (0·27–1.24)</td><td>0·179</td><td>1·000</td></tr>
<tr><td>Targeted therapy</td><td>0.56 (0·30–1.01)</td><td>0·058</td><td>0.525</td></tr>
<tr><td>Hormone therapy</td><td>1·16 (0·64–2·06)</td><td>0·659</td><td>1·000</td></tr>
<tr><td>Radiotherapy</td><td>0·66 (0·37–1·17)</td><td>0·178</td><td>1·000</td></tr>
</table>
Odds of death by therapy type based on multivariate regression analysis (corrected for age, sex and comorbidities) (all patients) (Lee et al, 2020a)
<table>
<tr><td>All-cause mortality</td><td>Odd ratio (95% CI)</td><td>p value</td></tr>
<tr><td>Chemotherapy vs no chemotherapy</td><td>1·18 (0·81–1·72)</td><td>0·380</td></tr>
<tr><td>Immunotherapy vs no immunotherapy</td><td>0·59 (0·27–1·27)</td><td>0·177</td></tr>
<tr><td>Targeted therapy vs no targeted therapy</td><td>0·83 (0·45–1·54)</td><td>0·559</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference/s	**COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study, Lee et al 2020a** **COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study, Lee et al 2020b**
	Hormone therapy vs no hormone therapy: 0·90 (0·49–1·68); 0·744 Radiotherapy vs no radiotherapy: 0·65 (0·36–1·18); 0·159 Odds of death by therapy type based on multivariate regression analysis (corrected for age and sex) (patients with haematological cancers) (Lee et al, 2020b) All-cause mortality: Odd ratio (95% CI); p value Chemotherapy vs no chemotherapy: 2.09 (1.09–4.08); 0·028
Additional results	Odds of death by type of chemotherapy based on multivariate regression analysis (corrected for age, sex and comorbidities) (Lee et al, 2020a) All-cause mortality: Odd ratio (95% CI); p value Non-palliative chemotherapy vs palliative chemotherapy: 0·40 (0·17–0·96); 0.040 Palliative first-line chemotherapy vs other line chemotherapy: 0·84 (0·36–1·98); 0.690 Palliative chemotherapy vs no chemotherapy: 1·48 (0·93–2·36); 0.102 Palliative chemotherapy vs no therapy: 1·05 (0·63–1·76); 0.854
Statistical Analysis	Multivariable logistic regression was used to estimate odd ratios and 95% CIs of each factor after adjusting for clinically relevant potential confounders (age, gender, diabetes, hypertension, chronic obstructive pulmonary disease, or other comorbidities at admission). Goodness of fit was checked using the Hosmer-Lemeshow test and had p>0·05. Further multivariable logistic regression models using the aforementioned potential confounders was done using a forward selection of p<0·10 where the goodness of fit criteria was not met. Patients with either no information or missing relevant data were excluded in these regression analyses. Subgroup analyses of patients on chemotherapy were undertaken for first-line versus later lines of palliative chemotherapy, non-palliative versus palliative chemotherapy, palliative chemotherapy versus no anti-cancer treatment, and palliative chemotherapy versus no recent chemotherapy within 4 weeks of admission. A subgroup analysis was also performed to compare all-cause mortality in people with haematological cancers who had received recent chemotherapy with people with haematological cancers who had not received recent chemotherapy (Lee et al, 2020b). Data are reported above.

Bibliographic reference/s	**COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study, Lee et al 2020a** **COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study, Lee et al 2020b**		
Risk of bias (ROB) QUIPS tool	Outcome	Judgement	Comments
	Study participation	Moderate	Baseline sample and recruitment clearly described. The sample is recruited from within the UK but it is unclear if the patients within this cohort are representative of all UK cancer patients or if there was something about them that pre-disposed them to COVID-19. For example, the Lee paper notes that the included patients are symptomatic and needing secondary care review for possible hospitalisation and so patients with cancer and asymptomatic COVID-19 would not be represented.
	Study attrition	Low	Attrition didn't occur due to short follow-up period (hospital discharge)
	Prognostic factor management	Moderate	Fairly well defined prognostic factors. Patients were assessed by local teams and review of their medical notes to determine whether they had received the specified anticancer treatments within 4 weeks of COVID-19 diagnosis. However, the granular detail about specific types of therapy is absent.
	Outcome measurement	Moderate	Outcome well defined but short follow-up period may not have captured all deaths
	Study confounding	Moderate	Important confounders were controlled for (for example, age, sex and comorbidities). Not possible to determine if the patients who received anticancer therapy were somehow different to those not receiving therapy. It is also unclear if they modified treatment regimens to be less immunosuppressive.
	Statistical analysis and reporting	Low	Statistical analyses seem appropriate. No apparent selective reporting of results.
	Overall Risk of Bias	Acceptable risk of bias	
Source of funding	University of Birmingham, University of Oxford		
Comments	N/A		
Additional references	Comment in the Lancet on Lee et al and Kuderer et al: Cancer and COVID-19: what do we really know? Poortmans PM, Guarneri V and Cardoso MJ. Lancet 2020.		

Kuderer et al. (2020)

Bibliographic reference/s	Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study, Kuderer et al 2020
Study name	COVID-19 and Cancer Consortium (CCC19)
Publication status	Published
Registration	NCT04354701
Study type	Cohort (some prospective but primarily retrospective)
Study dates	March 17 2020 to April 16 2020
Objective	To describe the clinical and demographic characteristics and COVID-19 outcomes in patients with cancer
Country/ Setting	USA, Canada or Spain
Cohort source	Contributing institutions in the CCC19
Participant numbers	1035 records entered into CCC19 database and 928 patients met inclusion criteria for analysis.
Population	Laboratory confirmed COVID-19. Patients aged 18 years or older with a current or past history of invasive solid tumour or haematological malignancy.
Prognostic factors	Chemotherapy, immunotherapy, endocrine therapy, targeted therapy, radiotherapy within 4 weeks of COVID-19 diagnosis
Baseline study sample characteristics	Some of the key characteristics are extracted below but please refer to full paper for details of other characteristics, particularly around cancer type and stage. All patients (n=928) Male 468 (50%) Median age, years 66 (57–76) 1 comorbidity 202 (22%) 2 comorbidities 231 (25%) 3 comorbidities 117 (13%) >=4 comorbidities 192 (21%) No comorbidities 132 (14%) Present, stable, or responding to treatment 294 (32%) Progressive disease 102 (11%) Remission 422 (45%) Cytotoxic systemic therapy* 160 (17%) Immunotherapy* 38 (4%) Targeted therapy* 75 (8%) Radiotherapy* 12 (1%) Endocrine therapy* 85 (9%) No cancer therapy* 553 (60%) * Within 4 weeks of COVID-19 diagnosis
Attrition	N/A. Although note there is missing data, notably 5% cancer status and 3% for comorbidities.

<table>
<tr><th>Bibliographic reference/s</th><td>Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study, Kuderer et al 2020</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with presumptive COVID-19 who did not have a laboratory confirmed SARS-CoV-2 infection were excluded due to possible confounding by other infections. Patients with non-invasive cancers including non-melanomatous skin cancer, in-situ carcinoma, or precursor haematological neoplasms were excluded from the analysis.</td></tr>
<tr><td>Data collection</td><td>Concurrent or retrospective (after the course of COVID-19).</td></tr>
<tr><td>Outcome measure</td><td>The primary outcome was all-cause mortality reported within 30 days of COVID-19 diagnosis.</td></tr>
<tr><td>Follow-up</td><td>30 days</td></tr>
<tr><td>Main results</td><td>Odds of death by therapy type, versus no anticancer treatment in 4 weeks before COVID-19 diagnosis, based on bivariable regression analysis
All-cause mortality — Odd ratio (95% CI)
Cytotoxic systemic therapy — 1·02 (0·61–1·69)
Non-cytotoxic therapy* — 0·80 (0·49–1·32)
*Non-cytotoxic therapy includes immunotherapy, targeted therapy, radiotherapy and endocrine therapy. All therapies given within 4 weeks of COVID-19 diagnosis.

Odds of death by therapy type based on multivariable regression analysis (corrected for age, sex, smoking status and obesity)
All-cause mortality — Odd ratio (95% CI)
Cytotoxic systemic therapy — 1·47 (0·84–2·56)
Non-cytotoxic therapy* — 1·04 (0·62–1·76)
*Non-cytotoxic therapy includes immunotherapy, targeted therapy, radiotherapy and endocrine therapy. All therapies given within 4 weeks of COVID-19 diagnosis.</td></tr>
<tr><td>Additional results</td><td>Descriptive outcomes
<table>
<tr><th></th><th>Died</th><th>Composite endpoint#</th><th>Admitted to ICU</th><th>Required mechanical ventilation</th></tr>
<tr><td>Cytotoxic systemic therapy</td><td>22 (14%)</td><td>35 (22%)</td><td>17 (11%)</td><td>12 (8%)</td></tr>
<tr><td>Non-cytotoxic therapy*</td><td>23 (11%)</td><td>50 (24%)</td><td>24 (12%)</td><td>24 (12%)</td></tr>
<tr><td>None</td><td>75 (14%)</td><td>156 (28%)</td><td>91 (16%)</td><td>79 (14%)</td></tr>
</table>
*Non-cytotoxic therapy includes immunotherapy, targeted therapy, radiotherapy and endocrine therapy. All therapies given within 4 weeks of COVID-19 diagnosis.
composite endpoint = death, severe illness requiring hospital admission, admission to an ICU, or mechanical ventilation.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td colspan="3">Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study, Kuderer et al 2020</td></tr>
<tr><td></td><td colspan="3">Please note there are additional data presented in the paper and supplementary material.</td></tr>
<tr><td>Statistical Analysis</td><td colspan="3">Multivariable regression analysis was partially adjusted for age, sex, smoking status, and obesity. Age was treated as a continuous variable with age 90 years and older transformed into 90 years for modelling. There was no adjustment for multiple comparisons. Goodness of fit was assessed using Harrell's C-statistic with 95% CIs determined using DeLong and colleagues' method. Post-hoc power analyses were undertaken for the recent surgery and anticancer treatment variables to examine the study effect size, which were deemed sufficient.</td></tr>
<tr><td>Risk of bias (ROB)
QUIPS tool</td><td colspan="3"></td></tr>
<tr><td></td><td>Outcome</td><td>Judgement</td><td>Comments</td></tr>
<tr><td></td><td>Study participation</td><td>Moderate</td><td>Baseline sample and recruitment clearly described, but unclear if the patients within this non-UK cohort are representative of UK cancer patients or if there was something about them that pre-disposed them to COVID-19. For example, it is noted by Kuderer that patients who were tested were generally symptomatic.</td></tr>
<tr><td></td><td>Study attrition</td><td>Low</td><td>Attrition unlikely to have occurred due to short follow-up period (30 days)</td></tr>
<tr><td></td><td>Prognostic factor management</td><td>Moderate</td><td>Fairly well defined prognostic factors. The granular detail about specific types of anticancer therapy is lacking. Unclear if cancer therapies representative of those delivered in the UK.</td></tr>
<tr><td></td><td>Outcome measurement</td><td>Low</td><td>Outcome well defined and 30 day follow-up should capture course of COVID-19 in many patients</td></tr>
<tr><td></td><td>Study confounding</td><td>Moderate</td><td>Important confounders were controlled for (for example, age, sex and obesity). Not possible to determine if the patients who received therapy were somehow different to those not receiving therapy. Also unclear if they modified treatment regimens to be less immunosuppressive.</td></tr>
<tr><td></td><td>Statistical analysis and reporting</td><td>Low</td><td>Statistical analyses seem appropriate. No apparent selective reporting of results.</td></tr>
<tr><td></td><td>Overall Risk of Bias</td><td colspan="2">Acceptable risk of bias</td></tr>
<tr><td></td><td colspan="3"></td></tr>
</table>

Bibliographic reference/s	Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study, Kuderer et al 2020
Source of funding	American Cancer Society, National Institutes of Health, and Hope Foundation for Cancer Research
Comments	
Additional references	Comment in the Lancet on Lee et al and Kuderer et al: Cancer and COVID-19: what do we really know? Poortmans PM, Guarneri V and Cardoso MJ. Lancet 2020.

Tian et al. (2020)

Bibliographic reference/s	Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study, Tian et al 2020
Study name	NA
Publication status	Published
Registration	Chinese Clinical Trial Register, ChiCTR2000030807
Study type	Cohort (retrospective)
Study dates	January 13 to March 18 2020
Objective	To characterise clinical features and determine risk factors of COVID-19 disease severity for patients with cancer and COVID-19.
Country/ Setting	China
Cohort source	9 hospitals in Wuhan
Participant numbers	232 patients with cancer out of 13,077 patients with COVID-19
Population	Laboratory confirmed COVID-19. Adults with malignant solid tumour or haematological cancer
Prognostic factor	Chemotherapy or radiotherapy, targeted therapy or immunotherapy
Baseline study sample characteristics	See paper for full details but non-cancer patients were matched to cancer patients, including on comorbidities age and sex

	Cancer patients (n=232)	Non-cancer patients (n=519)	p value
Male	51%	49%	0.57
Age (range), years	64 (58-69)	64 (56-70)	0.42
Current smoker	6%	6%	0.89
Hypertension	41%	38%	0.39
COPD	1%	<1%	0.17
Diabetes	24%	28%	0.31
Received chemotherapy or radiotherapy	214	NA	NA
Received targeted therapy or immunotherapy	32	NA	NA

<table>
<tr><td>Bibliographic reference/s</td><td>Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study, Tian et al 2020</td></tr>
<tr><td>Attrition</td><td>No cases lost to follow-up</td></tr>
<tr><td>Exclusion criteria</td><td>NR</td></tr>
<tr><td>Data collection</td><td>Retrospective</td></tr>
<tr><td>Outcome measure</td><td>COVID-19 severity. Severe disease classified as: respiratory rate of at least 30 breaths per min, oxygen saturation of 93% or lower in a resting state, ratio of arterial partial pressure of oxygen and oxygen concentration no greater than 300 mm Hg, or more than 50% lesion progression in lung imaging within 24–48 h</td></tr>
<tr><td>Follow-up</td><td>Defined as duration from hospital admission to outcomes (survivor or non-survivor)</td></tr>
<tr><td>Main results</td><td>Odds of COVID-19 severity by therapy type, versus surgery, based on univariable logistic regression analysis
*Timeframe of receipt of chemotherapy or radiotherapy is unclear for these overall data. Please note additional data broken down by timeframe of receipt are available in the appendix (not extracted here).

Odd ratio (95% CI; p value)
Chemotherapy or radiotherapy * 1·27 (0·85–1·89; p=0.25)
Targeted therapy or immunotherapy 2·84 (1·12–7·22; p=0.028)

Odds of COVID-19 severity by therapy type, versus surgery, based on multivariable logistic regression analysis (corrected for age, sex, tumour stage, cancer type and comorbidities)

Odd ratio (95% CI; p)
Chemotherapy or radiotherapy (n=214) * 1·28 (0·85–1·94; p=0.24)
Targeted therapy or immunotherapy (n=32) 3·29 (1·26–8·61; p=0.015)</td></tr>
<tr><td>Additional results</td><td>Please note there are additional data presented in the paper and supplementary material.</td></tr>
<tr><td>Statistical Analysis</td><td>Enrolled patients were statistically matched with patients admitted with COVID-19 without cancer using propensity score matching with an approximate ratio of 2:1 based on age, sex, and comorbidities Univariable and multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% CIs, adjusting for age, sex, comorbidities, cancer type, tumour stage, and antitumour treatments</td></tr>
<tr><td>Risk of bias (ROB)
QUIPS tool</td><td>
<table>
<tr><td>Outcome</td><td>Judgement</td><td>Comments</td></tr>
<tr><td>Study participation</td><td>Moderate</td><td>Baseline sample and recruitment are described. Unclear if the patients within this non-UK</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference/s	Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study, Tian et al 2020		
			cohort are representative of UK cancer patients or if there was something about them that pre-disposed them to COVID-19. For example, included patients were admitted to hospital with COVID-19 and so the sample may not be representative of patients with COVID-19 who were not admitted.
	Study attrition	Low	No cases were lost to follow-up
	Prognostic factor management	Moderate	The granular detail about specific types of therapy is lacking. The timeframe from receiving the cancer therapy is poorly described. Unclear if cancer therapies representative of those delivered in the UK
	Outcome measurement	Moderate	Outcome reasonably well defined
	Study confounding	Moderate	Important confounders were controlled for (for example, age and sex). Not possible to determine if the patients who received therapy were somehow different to those not receiving therapy. Also unclear if they modified treatment regimens to be less immunosuppressive
	Statistical analysis and reporting	Moderate	Methods reasonably well reported and no signs of selective reporting
	Overall Risk of Bias	Acceptable risk of bias	
Source of funding	China National Natural Science Foundation (grant number 81974400)		
Comments	N/A		
Additional references	N/A		

Zhang et al. (2020)

Bibliographic reference/s	Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China **Zhang et al 2020**
Study name	NA
Publication status	Published
Registration	N/A
Study type	Cohort (retrospective)
Study dates	January 13 to February 26 2020
Objective	To characterise clinical features and determine risk factors of COVID-19 disease severity for patients with cancer and COVID-19
Country/ Setting	China
Cohort source	3 hospitals in Wuhan
Participant numbers	28 patients with cancer out of 1,276 patients with COVID-19
Population	Laboratory confirmed COVID-19 infection. Patients with solid tumour
Prognostic factor	Chemotherapy, immunotherapy, targeted therapy, radiotherapy
Baseline study sample characteristics	See paper for full details Cancer patients (n=28) Male: 61% Median age (IQR), years: 65 (56-70) Diabetes: 4 (14%) Chronic cardiovascular and cerebrovascular disease: 4 (14%) Chronic pulmonary disease: 1 (4%) Stage 4 cancer: 10 (36%) Received chemotherapy within 14 days before diagnosis: 3 (11%) Received radiotherapy within 14 days before diagnosis: 1 (4%) Received targeted therapy within 14 days before diagnosis: 2 (7%) Received immunotherapy within 14 days before diagnosis: 1 (4%)
Attrition	NA
Exclusion criteria	NR
Data collection	Retrospective
Outcome measure	Severe clinical events defined as a condition requiring admission to an ICU, the use of mechanical ventilation, or death
Follow-up	NR

<table>
<tr><td>Bibliographic reference/s</td><td colspan="3">Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China
Zhang et al 2020</td></tr>
<tr><td>Main results</td><td colspan="3">Hazard ratio of severe events based on multivariate analysis
Hazard ratio (95% CI; p)
Last antitumour treatment within 14 days: 4.08 (1.086–15.322; p=0.037)</td></tr>
<tr><td>Additional results</td><td colspan="3">Please note there are additional data presented in the paper and supplementary material.</td></tr>
<tr><td>Statistical Analysis</td><td colspan="3">Hazard ratio (HR) and corresponding 95% CIs from the Cox proportional hazards model were calculated. The multivariate-adjusted Cox proportional hazards model was adjusted for age and sex.</td></tr>
<tr><td>Risk of bias (ROB)
QUIPS tool</td><td colspan="3"></td></tr>
<tr><td></td><td>Outcome</td><td>Judgement</td><td>Comments</td></tr>
<tr><td></td><td>Study participation</td><td>Moderate</td><td>Baseline sample described. Unlikely that patients within this non-UK cohort are representative of UK cancer patients. Unclear if there was something about them that pre-disposed them to COVID-19 infection. Patients were admitted to hospital and may not be representative of cancer patients with COVID-19 who were not admitted.</td></tr>
<tr><td></td><td>Study attrition</td><td>Moderate</td><td>Unclear loss to follow-up</td></tr>
<tr><td></td><td>Prognostic factor management</td><td>Moderate</td><td>The granular detail about specific types of therapy is lacking. Unclear if cancer therapies same as UK</td></tr>
<tr><td></td><td>Outcome measurement</td><td>Moderate</td><td>Outcome reasonably well defined</td></tr>
<tr><td></td><td>Study confounding</td><td>Moderate</td><td>Important confounders were controlled for (for example, age and sex).Not possible to determine if the patients who received therapy were somehow different to those not receiving therapy. Also unclear if they modified treatment regimens to be less immunosuppressive</td></tr>
<tr><td></td><td>Statistical analysis and reporting</td><td>High</td><td>Methods not well reported and unclear selective reporting</td></tr>
<tr><td></td><td>Overall Risk of Bias</td><td colspan="2">High risk of bias</td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td>Source of funding</td><td colspan="3">National Natural Science Foundation of China (No. 81700032, No. 81570348, and No. 81572934)</td></tr>
<tr><td>Comments</td><td colspan="3"></td></tr>
</table>

Bibliographic reference/s	**Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China** **Zhang et al 2020**
Additional references	Related studies (excluded at full text – see appendix 3) Zhang, Hongyan, Wang, Linwei, Chen, Yuanyuan et al. (2020) Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. Cancer Zhang, Hong-Yan, Wang, Lin-Wei, Chen, Yuan-Yuan et al. A Multicentre Study of 2019 Novel Coronavirus Disease Outcomes of Cancer Patients in Wuhan, China. medrxiv preprint Editorial from the Lancet: COVID-19 infection in cancer patients: early observations and unanswered questions. W.K, Oh

Evidence for the guideline in March 2020

Liang et al. (2020)

<table>
<tr><td>Bibliographic reference/s</td><td>Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Liang et al 2020</td></tr>
<tr><td>Study name</td><td>NA</td></tr>
<tr><td>Publication status</td><td>Published as a letter (unclear if peer reviewed)</td></tr>
<tr><td>Registration</td><td>NA</td></tr>
<tr><td>Study type</td><td>Cohort study</td></tr>
<tr><td>Study dates</td><td>Data cut-off January 31 2020</td></tr>
<tr><td>Objective</td><td>To describe the clinical and demographic characteristics and COVID-19 outcomes in patients with cancer</td></tr>
<tr><td>Country/ Setting</td><td>China</td></tr>
<tr><td>Cohort source</td><td>575 hospitals across China</td></tr>
<tr><td>Participant numbers</td><td>18 patients with history of cancer out of 1590 patients with COVID-19</td></tr>
<tr><td>Population</td><td>Laboratory confirmed COVID-19 infection. History of cancer</td></tr>
<tr><td>Prognostic factor</td><td>Chemotherapy plus surgery</td></tr>
<tr><td>Baseline study sample characteristics</td><td>Limited details available. Data taken from both editorial and supplementary data available online

<table>
<tr><td></td><td>Cancer patients (n=18)</td><td>Non-cancer patients (n=1572)</td><td>p value</td></tr>
<tr><td>Male</td><td>61.1%</td><td>57.2%</td><td>0.814</td></tr>
<tr><td>Age (range), years</td><td>63.1 (+-12.1)</td><td>48.7 (+-16.2)</td><td><0.001</td></tr>
<tr><td>Known smoking history</td><td>22.2%</td><td>6.8%</td><td>0.032</td></tr>
<tr><td>Any other comorbidity</td><td>22.2%</td><td>24.2%</td><td>1.00</td></tr>
<tr><td>Received chemotherapy or surgery within past month</td><td>4/18</td><td>NA</td><td>NA</td></tr>
</table></td></tr>
<tr><td>Attrition</td><td>N/A</td></tr>
<tr><td>Exclusion criteria</td><td>Insufficient records of previous disease history</td></tr>
<tr><td>Data collection</td><td>Unclear</td></tr>
<tr><td>Outcome measure</td><td>Severe events</td></tr>
<tr><td>Follow-up</td><td>Unclear</td></tr>
<tr><td>Main results</td><td><table><tr><td></td><td>Severe events n (%)</td><td>Odds ratio (95% CI)*</td><td>p value</td></tr></table></td></tr>
</table>

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<tr><td>Bibliographic reference/s</td><td colspan="3">Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Liang et al 2020</td></tr>
<tr><td></td><td colspan="3">
Chemotherapy or surgery in past month 3/4 (75%) 5.34 (1.80-16.18) 0.0026
Not received chemotherapy or surgery in past month 6/14 (43%)
*Logistic analysis adjusted for age, smoking and comorbidities
</td></tr>
<tr><td>Additional results</td><td colspan="3">Limited details in publication</td></tr>
<tr><td>Statistical Analysis</td><td colspan="3">Unclear methods</td></tr>
<tr><td>Risk of bias (ROB)
QUIPS tool</td><td colspan="3">
<table>
<tr><td>Outcome</td><td>Judgement</td><td>Comments</td></tr>
<tr><td>Study participation</td><td>High</td><td>Baseline sample not clearly described. Unclear if the patients within this non-UK cohort are representative of UK cancer patients or if there was something about them that pre-disposed them to COVID-19 infection. Patients were admitted to hospital and so may not be representative of patients with cancer and COVID-19 who were not admitted.</td></tr>
<tr><td>Study attrition</td><td>Moderate</td><td>Unclear loss to follow-up</td></tr>
<tr><td>Prognostic factor management</td><td>High</td><td>Poorly defined prognostic factors. The granular detail about specific types of therapy is lacking. Unclear if cancer therapies same as UK</td></tr>
<tr><td>Outcome measurement</td><td>High</td><td>Outcome not well defined</td></tr>
<tr><td>Study confounding</td><td>Moderate</td><td>Important confounders were controlled for but unclear methods (for example, age, smoking status). Not possible to determine if the patients who received therapy were somehow different to those not receiving therapy. Also unclear if they modified treatment regimens to be less immunosuppressive.</td></tr>
<tr><td>Statistical analysis and reporting</td><td>High</td><td>Unclear details of methods and reporting</td></tr>
<tr><td>Overall Risk of Bias</td><td colspan="2">High risk of bias</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference/s	**Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Liang et al 2020**
Source of funding	Not reported
Comments	
Additional references	The following replies highlight some of the issues with this study: Correspondence Risk of COVID-19 for patients with cancer. Xia et al. Lancet 2020 Correspondence Risk of COVID-19 for patients with cancer. Wang and Zhang. Lancet 2020

Appendix 5 GRADE profiles

Profile 1: All-cause mortality with chemotherapy within past 4 weeks, based on multivariate analysis

Quality assessment							No of patients		Effect (multivariate analysis)		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exposed to chemo	No chemo	Odds (95% CI)	Absolute	
All-cause mortality (in hospital), adjusted for age, sex, diabetes, hypertension, COPD, or other comorbidities at admission (all patients)											
1 (Lee 2020a)	Cohort	serious[1]	serious[2]	no serious	serious[3]	None	281/800 (35%)	519/800 (65%)	OR 1.18 (0.81 to 1.72)	Not reported	⨁⨁OO LOW
All-cause mortality (in hospital), adjusted for age and sex (patients with haematological cancers only)											
1 (Lee 2020b)	Cohort	serious[1]	serious[2]	no serious	serious[3]	None	108/227 (48%)	119/227 (52%)	OR 2.09 (1.09 to 4.08)	Not reported	⨁⨁OO LOW
All-cause mortality (30 days), adjusted for age, sex, smoking status and obesity											
1 (Kuderer)	Cohort	serious[1]	serious[2]	serious[4]	serious[3]	None	160/928 (17%)	768/928 (83%)	OR 1.47 (0.84 to 2.56)	Not reported	⨁OOO VERY LOW

1 Downgraded based on QUIPS risk of bias assessments. See data extraction sheets for more details

2 Downgraded as only 1 study so cannot assess

3 Wide confidence intervals

4 Not UK population so cannot be certain therapies given to patients were consistent with the UK in terms of cancer therapies and COVID-19 therapies

Profile 2: All-cause mortality with radiotherapy within past 4 weeks, based on multivariate and univariate analyses

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exposed to radio	No radio	Odds (95% CI)	Absolute	
All-cause mortality (in hospital), multivariate analysis adjusted for age, sex, diabetes, hypertension, COPD, or other comorbidities at admission											
1 (Lee 2020a)	Cohort	serious[1]	serious[2]	no serious	serious[3]	none	76/800 (10%)	724/800 (90%)	OR 0.65 (0.36 to 1.18)	Not reported	⊕⊕OO LOW

1 Downgraded based on QUIPS risk of bias assessments, see data extraction sheets for more details

2 Downgraded as only 1 study so cannot assess

3 Wide confidence intervals

Profile 3: All-cause mortality with immunotherapy within past 4 weeks, based on multivariate and univariate analyses

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exposed to immuno	No immuno	Odds (95% CI)	Absolute	
All-cause mortality (in hospital), multivariate analysis adjusted for age, sex, diabetes, hypertension, COPD, or other comorbidities at admission											
1 (Lee 2020a)	Cohort	serious[1]	serious[2]	no serious	serious[3]	none	44/800 (6%)	756/800 (94%)	OR 0.59 (0.27 to 1.27)	Not reported	⊕⊕OO LOW

1 Downgraded based on QUIPS risk of bias assessments, see data extraction sheets for more details

2 Downgraded as only 1 study so cannot assess

3 Wide confidence intervals

Profile 4: All-cause mortality with targeted therapy within past 4 weeks, based on multivariate and univariate analyses

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exposed to targeted	No targeted	Odds (95% CI)	Absolute	
All-cause mortality (in hospital), multivariate analysis adjusted for age, sex, diabetes, hypertension, COPD, or other comorbidities at admission											
1 (Lee 2020a)	Cohort	serious[1]	serious[2]	no serious	serious[3]	none	72/800 (9%)	728/800 (91%)	OR 0.83 (0.45 to 1.54)	Not reported	⊕⊕OO LOW

1 Downgraded based on QUIPS risk of bias assessments, see data extraction sheets for more details

2 Downgraded as only 1 study so cannot assess

3 Wide confidence intervals

Profile 5: All-cause mortality with hormone therapy within past 4 weeks, based on multivariate analysis

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exposed to hormone	No hormone	Odds (95% CI)	Absolute	
All-cause mortality (in hospital), multivariate analysis adjusted for age, sex, diabetes, hypertension, COPD, or other comorbidities at admission											
1 (Lee 2020a)	Cohort	serious[1]	serious[2]	no serious	serious[3]	none	64/800 (8%)	736/800 (91%)	OR 0.90 (0.49 to 1.68)	Not reported	⊕⊕OO LOW

1 Downgraded based on QUIPS risk of bias assessments, see data extraction sheets for more details

2 Downgraded as only 1 study so cannot assess

3 Wide confidence intervals

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