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TITLE:

Timely initiation of chemotherapy.. a systematic literature review in six priority cancers – results and recommendations for clinical practice

ABSTRACT:

This review evaluated the association between time-to-chemotherapy (TTC) and survival in six priority cancers. A systematic review of the literature was undertaken for papers indexed in MEDLINE and Cochrane Library databases from earliest index until April 2014. The methodology used has been published in a separate paper (Timely initiation of chemotherapy. Part 1: a proposed framework for access to medical oncology and haematology cancer clinics and chemotherapy services). The optimal timing of chemotherapy in breast cancer is unclear as available studies are of low quality, report inconsistent results, and are limited to the adjuvant setting. However, increased TTC may have a negative prognostic impact and delays beyond 4 weeks should be avoided. Studies suggest that the optimal timing for initiation of adjuvant chemotherapy for surgically resected colorectal cancer is 4–8 weeks post-surgery. Timing of chemotherapy for metastatic colorectal cancer does not influence survival. There is a paucity of studies to guide the timing of chemotherapy for the treatment of lymphoma and myeloma; no definitive conclusions can be drawn and clinician discretion should be applied. The optimal timing of chemotherapy in lung cancer is unclear; however, rapid tumour growth and poor disease prognosis suggest that delays should be avoided wherever possible. The optimal timing of chemotherapy in ovarian cancer is unclear as available studies are of low level, report inconsistent results, and are limited to the post surgery setting; however, increased TTC may have a negative prognostic impact, therefore; delays beyond 4 weeks should be avoided.

KEYWORDS: Cancer, Chemotherapy, Drug Therapy, Quality Indicator, Timely

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Introduction:

Timely initiation of chemotherapy should be informed by the best available evidence. This review was conducted to determine whether delayed chemotherapy initiation results in reduced survival outcomes in patients receiving systemic chemotherapy for the treatment of breast, colorectal, lung or ovarian cancer and lymphoma or myeloma by systematically searching the published literature.

Current international guidelines recommend (and publically report performance against) a maximum time to treatment (for any treatment modality) of four weeks from decision-to-treat for any anticancer therapy.¹⁻³ At the time of undertaking this review, in Victoria and across Australia, frameworks providing guidance for the appropriate timeliness of care were available for surgery and radiotherapy treatment modalities.^{4,5} However, equivalent guidance for chemotherapy was lacking.

Updated Australian cancer optimal care pathways are available.⁶ Although not specific for chemotherapy, they do include recommendations relating to timeliness of care. For colorectal cancer the maximum recommended interval from the development of a management plan to chemotherapy initiation was 3 weeks for neoadjuvant chemotherapy and 3 months for adjuvant chemotherapy.⁷ For lung cancer, a maximum interval of 6 weeks from initial specialist referral to initial treatment was recommended.⁸ While the updated ovarian cancer pathway was available only in draft form at the time of writing, it was recommended that chemotherapy should be initiated within 4 weeks of the decision to treat with chemotherapy.⁹ Updated pathways for breast cancer and lymphoma were not available. However, a previous version of the breast cancer pathway¹⁰ recommended that surgical review should occur within 2 weeks of general practitioner referral; no recommendations relating to timeliness of treatment generally or chemotherapy more specifically were made and a previous version of the pathway for non-Hodgkin's lymphoma (NHL) did not contain any recommendations for the timeliness of chemotherapy initiation.¹¹ Optimal care pathways for other lymphomas and myeloma have not been published, highlighting the importance of the current review in guiding local practice and health policy.

This review of time-to-chemotherapy (TTC) in cancer was undertaken to inform healthcare policy across hospitals in Victoria Australia and helped in the development of guidelines for the timely initiation of chemotherapy (available on <http://health.vic.gov.au/cancer/framework/chemotherapy-guidelines.htm>).

Methods:

The methods used for this systematic review are outlined in the position paper (Timely initiation of chemotherapy. Part 1: a proposed framework for access to medical oncology and haematology cancer clinics and chemotherapy services), published separately [insert citation]. However, in brief, the MEDLINE and Cochrane Library databases were searched for articles, published in the English language from earliest index to April 2014, presenting data on the association between TTC and survival in six priority cancers (breast, colorectal, lung [non-small cell and small cell], ovarian cancer or lymphoma and

myeloma). The reference lists of articles identified by the literature search were also reviewed for additional publications. Google® and Google Scholar® were also searched to identify non-indexed grey literature regarding lymphoma and myeloma. All titles and abstracts were then manually screened and studies that did not meet the inclusion criteria were omitted. The quality of the published studies was assessed using standard protocols from the National Health and Medical Research Council of Australia and, where relevant, the Newcastle Ottawa Scale for assessing the quality of nonrandomised studies (Table 2).^{12, 13}

Breast Cancer:

The search strategy yielded 1659 results; 1537 from MEDLINE, 112 from the Cochrane Library and an additional 10 papers from reference list review. Of these, nine papers were included in the final review to answer the question of whether TTC impacts on survival outcomes in breast cancer. All studies reported outcomes based on the TTC interval from date of surgery to commencement of adjuvant chemotherapy.¹⁴⁻²² No studies were available in the setting of neoadjuvant or palliative chemotherapy – a notable evidence gap. As described in Table 2, studies varied by publication date (1982–2014) and size ($n = 77$ – $34,097$), and reported data for a heterogeneous group of patients (stages I–IV). Study outcomes are detailed in Table 3. Five of 9 studies reported a significant association between delayed TTC and increased risk of death.

A single randomised controlled trial addressing the prognostic influence of early or delayed adjuvant chemotherapy in advanced breast cancer was identified.²¹ Whilst the generalisability of this study is poor (first published 1977) it provided the highest level of evidence (level II) in the adjuvant setting. A total of 75 premenopausal women with recurrent advanced breast cancer (not amenable to surgical or radio-therapeutic control) to early (<3 weeks post-surgery) or delayed (commence at disease progression) chemotherapy post oophorectomy.²¹ Early treatment was associated with longer progression free survival (53 versus 17 weeks, $p = 0.01$) however this did not translate to overall survival benefit. Whilst providing the highest level of evidence, this study has limited generalisability due to the age of the study, use of superseded chemotherapy regimen (5-fluorouracil, cyclophosphamide and prednisone) and restricted range of alternate systemic treatments (compared to those currently available) in the event of relapse or progression.

The largest body of evidence came from a 2013 meta-analysis which included seven studies with nine independent analytical groups and more than 34,000 participants.²² Pooled results demonstrated reduced overall (7 studies) and disease-free survival (2 studies) with each 4-week delay to commencement of adjuvant chemotherapy; hazard ratio (HR) for death 1.15 (95%CI 1.03–1.28) and HR for progression 1.16 (95%CI 1.01–1.33). This meta-analysis presented level III-2 evidence, based on the lowest level of evidence from included studies. The quality of evidence varied from post hoc evaluations of randomised control trial data (patients not randomised according to TTC),^{23, 24} to the analysis of prospectively²⁵ and retrospectively²⁶⁻²⁹ collected institutional or registry data. Studies were conducted between 1989 and 2013 and all patients received anthracycline-based chemotherapy. Earlier studies did

not include use of agents such as taxanes which are now a standard of care and it is unclear how this might otherwise have influenced the data. TTC ranged from 2 to 12 weeks. Some individual studies demonstrated no survival impact with TTC up to 3 months;^{26, 29} however this result was not maintained in the analysis of pooled data.

Five of eight studies analysing institutional or registry data sets (level III-2 evidence) demonstrated no survival impact of TTC with maximum delay intervals of 35 days,^{18, 19} 9 weeks,¹⁷ and 3 months.³⁰ Of those reporting negative prognostic impact of delayed TTC,^{14, 16, 20, 31} reduced survival was observed at measured delay interval of greater than 45 days,¹⁶ 60 days,¹⁴ 70 days,¹⁵ and 98 days.²⁰ Reduced survival was demonstrated among all breast cancer patients in two studies,^{15, 16} whilst limited to subgroups in the other two studies.^{14, 20} Patient subgroups demonstrating worse survival with longer TTC included those with the poorest prognosis, grade III disease, trastuzumab treated human epidermal growth factor receptor 2 positive (HER2+) or triple negative breast cancers.^{14, 20}

Implications for practice

With overall inconsistent results from low grade evidence, the optimal timing of adjuvant chemotherapy remains unclear. However, based on the available body evidence in patients with breast cancer, with particular weighting to the largest body of data from the recently completed meta-analysis, it is recommended avoiding delays beyond 4 weeks in all patients receiving adjuvant therapy for breast cancer due to a likely association with reduced overall survival. It appears that patients with high risk disease (triple negative, HER2+ or high grade disease) are most likely to derive benefit from earlier TTC so for these patients it is recommended that chemotherapy commence as soon as possible.

Without a single study to guide practice, the impact of TTC in the setting of neoadjuvant or palliative chemotherapy remains unknown. Treatment in this setting is often associated with more aggressive or advanced disease or with a known biology of poor prognosis. However, expert opinion is that treatment in these settings should commence as for high risk breast cancers in the adjuvant setting as soon as possible and within 4 weeks. Early treatment commencement aims to prevent tumour growth and spread, preserve quality of life, and protect viability of future treatment options.

Colorectal Cancer:

The search strategy yielded 741 results; 661 from MEDLINE, 75 from the Cochrane Library and an additional five papers identified from reference lists. Of these, seven papers were included in this review.³²⁻³⁸ Studies evaluated TTC intervals from diagnosis to systemic chemotherapy in the setting of metastatic disease,^{34, 35} and from surgery to systemic chemotherapy in the setting of curable disease.^{32, 33, 36-38} No studies evaluating TTC in the neoadjuvant setting were identified. This presents a significant evidence gap with combined modality chemoradiotherapy a standard treatment for locally advanced disease.³⁹ All studies were published within the last 10 years (2005–2014) and varied in size (n = 84–15,410). Populations included patients with both colon and rectal cancers and with curable and

metastatic disease (stages I–IV)[Table 4]. Four studies reported a significant association between delayed TTC and worse survival outcomes (Table 5).^{32, 33, 37, 38}

Two meta-analyses each including more than 13,000 patients receiving adjuvant chemotherapy demonstrated worse survival outcomes with longer TTC.^{32, 33} Analysing TTC at a defined 8 week time interval (n = 13,158) demonstrated that TTC beyond 8 weeks (compared with 8 weeks or less) was associated with an increased risk of death (Relative Risk (RR) 1.20, (95%CI) 1.15–1.26). With TTC analysed as a continuous variable (n = 15,410), each 4-week increment in TTC increased the risk of death (Hazard Ratio (HR) 1.14, 95%CI 1.10–1.17) and relapse (HR 1.14, 95%CI 1.10–1.18).³²

Two retrospective series further support findings of poorer survival outcomes with TTC beyond 8 weeks.^{37, 38} A study including 209 patients with colorectal cancer reported a 3-fold increased risk of death with TTC >8 weeks compared with <8 weeks (HR 3.28, 95%CI 1.17–9.2).³⁸ This study included both laparoscopic and open surgery, with TTC significantly shorter for laparoscopic procedures (52 vs 58 days, p = 0.008). However, there was no significant difference in 5-year overall survival for laparoscopic compared with open surgery (82% versus 80%, p = 0.05). While the entire cohort was skewed to early stage disease (85% stage I–II), TTC cohorts were well balanced in respect to age, gender, TNM stage, tumour grade and lymphovascular invasion. The second study included 355 patients with colorectal cancer and reported on the impact of post-operative complications and TTC.³⁷ In this patient group TTC beyond 8 weeks, (compared with <8 weeks and independent of postoperative complications), increased the risk of death (p = 0.001), local recurrence (p = 0.018) and distant recurrence (p = 0.017). Another retrospective study analysed patients with TTC up to a maximum of 6 weeks finding no significant difference in overall survival or relapse free survival at measured TTC intervals of 0–2 weeks, 3–4 weeks or 5–6 weeks (p > 0.2).³⁶

Two studies reported survival outcomes for patients with metastatic colorectal cancer with immediate (treat at diagnosis) or delayed (treat when symptomatic) chemotherapy initiation.^{34, 35} A meta-analysis including 84 patients from two randomised controlled trials (National Health and Medical Research Council [NHMRC] level I evidence) found no difference in overall survival, time to progression or quality of life with immediate versus delayed chemotherapy.³⁴ The HR for death and progression with immediate versus delayed chemotherapy was 1.15 (95% CI 0.77–1.72) and 1.08 (95% CI 0.71–1.64) respectively. Patients randomised to immediate treatment received chemotherapy within 1 month whilst the median TTC for the delayed cohorts was 4–6 months. Importantly the two studies were conducted in Canada and Australasia, with patients and treatments highly representative of the Victorian setting. The second study whilst presenting lower level of evidence (NHMRC level III-2) is highly applicable as analyses prospectively collected data from four Victorian hospitals.³⁵ This study included 736 patients receiving immediate (n = 377) or delayed (n = 192) chemotherapy for newly diagnosed metastatic colorectal cancer. The median TTC for the delayed cohort was 3.7 months. Among this study population, there was a reduced risk of death with delayed (median delay 3.7 months) versus immediate chemotherapy (HR 0.68, 95%CI 0.54–0.85). This reflects the better prognostic profile of patients assigned to delayed treatment within the clinical practice setting of this study: those who

received delayed treatment had better performance status, lower incidence of metastatic disease at diagnosis and lower incidence of multiple sites of distant metastasis compared with patients treated immediately.

Implications for practice

While there was no evidence to support a recommendation in the neoadjuvant setting of colorectal cancer, this review suggests that delays should be avoided to maximise outcomes as part of an aggressive multimodality treatment. However, in the interests of standardised care, it is suggested that initiation of neoadjuvant chemotherapy occur within 3 weeks as recommended by newly released Australian cancer care plans.⁷

Adjuvant treatment studies consistently demonstrate negative survival impact of delayed TTC >8 weeks,^{33, 37, 38} however, the optimal timing within this period remains unclear with one study finding that TTC >4 weeks is associated with reduced overall survival.³² Based on the largest body of evidence it is recommended that adjuvant chemotherapy should commence as soon as the patient is medically fit following surgery and within 8 weeks of surgery (level III, grade C).

The two available studies in advanced disease^{34, 35} are of high quality, have consistent findings, and are of high generalisability to the Victorian clinical practice setting. Based on the meta-analysis of randomised controlled trials (and supported by the local study), it is recommended that treatment commence based on clinician discretion and according to patient symptoms (level I, grade B).

Lymphoma and Myeloma:

The search strategy was performed separately for lymphoma and myeloma, yielding 386 and 175 results respectively. From these results, only two relevant studies were identified for lymphoma and none for myeloma. The two relevant studies were conducted in cohorts of patients with diffuse large B-cell lymphoma (DLBCL)⁴⁰ and Hodgkin's lymphoma (HL).⁴¹ These retrospective cohort studies (level III evidence) demonstrated no survival difference with TTC beyond 4 weeks in the DLBCL cohort and beyond 8 weeks in the HL cohort. Study design, patient cohorts and summary results are summarised in Table 6.

A single-centre retrospective study of 278 patients with DLBCL found that initiation of chemotherapy (measured from date of first haematology consult) beyond 4 weeks was not associated with reduced overall survival.⁴⁰ The study compared survival among patients with TTC of <1 weeks, 1–4 weeks and >4 weeks with no significant differences among the treatment groups. The median TTC interval was 3 weeks. However, the retrospective study design, lack of randomisation and small sample size severely compromises the ability of this study to inform clinical practice.

Evidence from a Canadian registry-based retrospective study of 879 patients with HL suggests that initiation of chemotherapy (measured from date of diagnosis) beyond 8 weeks is associated with a

reduced overall survival.⁴¹ Patients received at least one cycle of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) with curative intent within 2 weeks (13%), 3–4 weeks (30%), 5–8 weeks (46%) and >8 weeks (12%). The 5-year survival rate among patients initiating chemotherapy >8 weeks was significantly lower among those initiating chemotherapy within 2 weeks, (84 vs 90%; $p = 0.012$). There was no survival difference observed with other TTC intervals.

Due to the overall paucity of studies in patients with lymphoma or myeloma identified for this review, some studies that were previously excluded during the screening process were considered to provide additional guidance. Randomised controlled trials in indolent lymphomas and early stage myeloma have demonstrated that the timing of chemotherapy relative to disease course (i.e. at diagnosis or sometime later) does not impact on patient survival.^{42–47} Consequently it can be inferred that the TTC interval (measured from decision to treat with chemotherapy), while representing only a small portion of the overall observation interval, would also have no impact on patient survival.

A recent Canadian registry-based study (not included in this review as it was published outside of search dates) represents high quality evidence and supports the limited evidence included in this review. Multivariate analysis of 689 patients with DLBCL showed that TTC >8 weeks was associated with worse overall survival (HR 1.20 (95% CI 1.03–1.41), $p = 0.020$), progression-free survival (HR 1.33 (95% CI 1.15–1.54), $p < 0.001$), and disease-specific survival (HR 1.40 (95% CI 1.10–1.78), $p = 0.006$). The authors concluded that clinicians should endeavour to initiate curative chemotherapy as soon as possible after a diagnosis of DLBCL is established.⁴⁸

Implications for practice

We identified no studies in highly aggressive lymphomas (e.g. Burkitt's lymphoma, lymphoblastic lymphoma) or urgent presentations of other lymphomas or myeloma. Therefore, best clinical judgement must guide clinical practice. All patients require immediate referral and treatment with every hour delay potentially increasing the risk of mortality.

In the setting of aggressive and potentially curable lymphomas (e.g. DLBCL or NHL with non-urgent presentation), clinical intuition dictates the commencement of treatment as soon as possible. However, two studies^{40, 41} included in this review demonstrate no adverse survival outcomes with TTC beyond 4 and 8 weeks. These results should be interpreted with caution given the low number of studies and low level of evidence (level III). The overall majority of patients commenced treatment within 4 weeks (75% of DLBCL cohort and 43% of HL cohort), and this interval was felt to be most representative of the general lymphoma population, and therefore associated with less bias than the open ended TTC cohorts of >4 weeks or >8 weeks.

Noting that clinically unstable patients with urgent symptoms may require immediate commencement of treatment (as for highly aggressive lymphoma), this review suggests that in clinically stable patients a TTC interval of up to 4 weeks is acceptable (level III, grade C). Also, TTC for patients with indolent lymphomas or early stage myelomas should not be measured against any pre-defined interval rather,

based on the findings of randomised controlled trials demonstrating no survival impact for early chemotherapy versus observation, chemotherapy should commence based on the haematologist's discretion and according to the patient's symptoms (level II, grade C).

Lung Cancer:

The search strategy yielded 598 results; 514 from MEDLINE, 72 from the Cochrane Library and an additional 12 papers were identified from reference lists. Of these, 11 papers⁴⁹⁻⁵⁹ were reviewed. Studies varied by publication date (2000–2013) and size ($n = 21$ –10,583), and reported data for a heterogeneous group of patients (stages I–IV non-small cell lung cancer [NSCLC] and limited and extensive stage small cell lung cancer [SCLC]) as shown in Table 7 and Table 8. All identified studies were either prospective or retrospective observational studies which represents low level (level III-2) evidence.⁶⁰ Association between delay in TTC and negative patient outcomes was demonstrated in three studies.⁴⁹⁻⁵¹

All three studies in SCLC retrospectively evaluated either institutional^{56,58} or registry datasets.⁵⁷ No study reported an association between TTC and negative patient outcomes. Results are summarised in Table 9 and Table 10.

Two studies utilised positron emission tomography–computed tomography (PET-CT) scans to measure tumour growth while patients with inoperable NSCLC were waiting to commence definitive treatment in.^{49,50} These two imaging studies demonstrated disease progression (necessitating change to palliative therapy) in approximately one-quarter of patients (21% and 29%) waiting to commence definitive treatment.^{49,50} In the larger Australian study ($n = 82$), with a median 22 day scan interval, across all patients mean tumour volume nearly doubled (105cc versus 198cc).⁴⁹ Survival analyses in the Australian study were undertaken according to treatment intent with palliative treatment associated with almost 90% increased risk of death (Hazard Ratio (HR) for death with definitive versus palliative treatment 0.116; 95% CI: 0.025–0.527). While it is true that tumour growth within the scan interval (treatment delay) necessitated change to palliative treatment, survival analyses were not conducted according to scan interval (i.e. below or above the median or as continuous variable). It therefore remains uncertain whether progression occurred rapidly due to unfavourable biology or whether progression occurred purely as a consequence of excessive delay to treatment. In the UK study which had a notably smaller sample size ($n = 29$), with median 54 day scan interval >50% tumour growth was observed in 21% of patients and 20–50% tumour growth in another 21% of patients.⁵⁰ This study was unable to demonstrate a significant association between tumour growth and delay ($p = 0.06$); however, with >40% of patients experiencing >20% tumour growth it is likely that this represents limitations of statistical power rather than clinical significance. Conceptually these studies provide valuable data about tumour growth whilst waiting to commence any anticancer treatment. In the context of evaluating TTC, these studies are reflective of the interval to chemotherapy initiation where chemotherapy is part of the primary treatment plan in the setting of inoperable disease.

The five studies evaluating TTC in the setting of inoperable NSCLC included highly heterogeneous patient cohorts including patients with stage I–IV disease (adjusted for within survival analyses).^{51–54, 59} Although chemotherapy regimens were poorly reported (Table 9), the use of chemotherapy presumably included both curative and palliative intent therapies. A further limitation of these studies is inclusion of all treatment modalities rather than chemotherapy specifically. The proportion of patients receiving chemotherapy as their first treatment (alone or in combination with radiotherapy) ranged from 25% to 69%. No study demonstrated an association between TTC and survival among the entire when considering TTC intervals from 30 days to 6 months, or by per day analyses.^{51–54, 59} One study did show improved survival with early TTC; however, only in the subgroup of patients with overall survival ≥ 5 years.⁵¹ In this group a small but statistically significant increased risk of mortality was observed with each day chemotherapy was delayed (HR for death 1.029, 95%CI 1.003–1.005, $p = 0.029$).⁵¹

A single study investigated the impact of TTC in the adjuvant setting.⁵⁵ TTC was defined as time from surgery to chemotherapy commencement. This Canadian registry study, which analysed data on 1032 patients with NSCLC, reported no difference in overall survival for patients with early or delayed adjuvant chemotherapy. Analysis was undertaken with TTC as a continuous variable (Odds Ratio (OR) for death per day delay 1.00, 95%CI 0.99–1.00) and with a cut-off of TTC ≤ 10 weeks versus 11–16 weeks (4-year overall survival 64 versus 61%, $p=0.758$). Notably 35% of patients had TTC >10 weeks with approximately 10% treated in weeks 15 and 16. With more than a third of patients commencing chemotherapy beyond 10 weeks, findings at this cut-off are likely to be representative of the overall cohort and not specific to outliers with favourable/unfavourable disease. Despite being a well conducted study with large numbers and robust analyses, it remains a low level evidence source without supporting studies. It was therefore considered unreasonable to base clinical practice recommendations on this study alone.

Trials of adjuvant chemotherapy in NSCLC were not included in the current review as these studies evaluate the efficacy of chemotherapy rather the impact of TTC and thus did not fulfil the search criteria. However, the authors considered TTC intervals within five of the largest adjuvant chemotherapy studies as identified from a recent meta-analysis.⁶¹ Four studies specified maximal TTC intervals for study inclusion which ranged from 42^{62–64} to 60 days; ⁶⁵ maximal TTC for the fifth study was unclear as median TTC was reported as 48 days.⁶⁶

TTC in the setting of limited or extensive stage SCLC has not been demonstrated to impact on overall survival.^{56–58} One study actually demonstrated an inverse relationship with poorer outcomes for those with the shortest TTC interval,⁵⁷ likely reflecting the more urgent treatment of patients with significant symptoms and poor tumour biology. All three studies including patients with SCLC conducted survival analyses using alternate definitions of TTC: from first doctor visit, first oncologist visit or first abnormal radiograph (Table 10). This explains the large variance in TTC threshold utilised for survival analysis (<15 days vs >15 days compared with <42 days vs >42 days). When comparing similar TTC intervals across the three studies (not necessarily used in survival analyses), variance is reduced and intervals are shorter;

median diagnosis to treatment interval was 6 days,⁵⁷ 13 days⁵⁸ and median oncologist to treatment interval was 15 days.⁵⁶

Implications for practice

Due to a limited body of evidence directly evaluating TTC in the adjuvant setting (single level III study), it is recommended that adjuvant chemotherapy commence within 6–8 weeks of surgery based on the interval within adjuvant clinical trials. It is reasonable to apply the longer interval (8 weeks) based on the findings from the large registry study which demonstrated no survival impact with delays further beyond this time (level III, grade C).

Recommendations for the timely initiation of chemotherapy in inoperable NSCLC are primarily based on findings from the two prospective imaging studies, due to potential biases introduced by the mixed treatment settings in the retrospective studies. Avoiding treatment delays beyond 3 weeks (the median delay interval in the larger of the two imaging studies demonstrating significant tumour growth while waiting for treatment) are recommended (level III, grade C). While this review focuses on TTC, it is acknowledged that multimodality therapy requires timely access to both treatment modalities, and that in the clinical setting it is likely that timely access to radiotherapy is most difficult to achieve and will ultimately determine overall timeliness of care. Extrapolating tumour growth findings from the curative setting, a 3-week TTC interval is also deemed appropriate for the palliative treatment setting. Consistent recommendations for timely initiation of treatment in both curative and palliative settings are also considered advantageous for the purposes of providing a standardised care to all patients.

Patients with SLCL presenting with severe or life threatening symptoms (e.g. superior vena cava obstruction) should be regarded as a medical emergency. Such patients should be supported and managed symptomatically. Upon appropriate investigations, including biopsy and staging, chemotherapy should be commenced immediately. Outside of an emergency presentation, studies from clinical practice settings have demonstrated that patients with SCLC routinely commence chemotherapy rapidly (within 6–15 days) from the time of diagnosis or oncologist review.^{56–58} This is sensible practice given rapid progression in the absence of treatment. To prevent progression and maximise outcomes, it is recommended that patients with SCLC should commence chemotherapy as soon as possible, and in line with currently reported practice, within 2 weeks from ready-for-care.

Ovarian Cancer:

The search strategy yielded 213 results; 169 from MEDLINE, 40 from the Cochrane Library and an additional 4 papers identified from reference lists; of these, 10 papers were reviewed. All studies evaluated TTC in the first-line post surgery setting with no studies in the setting of neoadjuvant chemotherapy or no planned surgery. While most ovarian cancer patients will undergo surgery, this is a notable evidence gap with no scientific foundation from which to inform the timely initiation of chemotherapy in these settings. Studies varied by publication date (1995–2014) and size (n = 191–

3326), and reported data for a heterogeneous group of patients (stages I–IV). Study designs and patient populations are summarised in Table 11 and results are presented in Table 12.

A recent meta-analysis included data from three randomised trials ($n = 3326$).⁶⁷ The trial populations included patients with stage IIB–IV ovarian cancer with no restriction on age (range 19–83 years). Across the included studies no chemotherapy treatment arm demonstrated a survival advantage meaning that data could be pooled and used to evaluate the effect of other prognostic indicators including TTC. Importantly patients were not randomised by TTC and the studies are therefore considered level III evidence.⁶⁰ TTC was analysed as a continuous variable and a significant association between delayed TTC and worse survival outcomes were demonstrated only for patients with no residual disease. In this population delayed TTC was associated with a modest (0.5 to 8.7%) increase in risk of death per week delay (HR for death per week delay 1.087, 95%CI 1.005–1.176). No effect on progression free survival was demonstrated. Among patients with residual disease, although TTC was not associated with survival, delayed TTC was associated with later progression (HR for progression per week delay: 0.931, 95% CI 0.895–0.969). While these results are statistically significant, the 95% CI approaches the null value both for risk of death and progression. It should also be noted that individual studies within and outside of this meta-analysis fail to demonstrate any relationship between TTC and survival.

A second meta-analysis included data from four interventional trials ($n = 472$).⁶⁸ The trial population included patients with stage IIB–IV ovarian cancer with no restriction on age (range: 22–85 years). Pooled data for the TTC analysis was stratified by the interventional study arm to remove the influence of the different interventional study drugs and doses. As described above, patients were not randomised by TTC and the studies are therefore considered level III evidence.⁶⁰ This study evaluated the impact of TTC below and above the median interval (<22 vs ≥ 22 days). The interquartile and overall range of TTC was 14–30 days and 5–113 days respectively. The presence of bulky residual disease post-surgery (a negative prognostic indicator) was associated with earlier TTC. The impact of this is seen in univariate analysis of TTC demonstrating a trend of worse progression free survival in patients with early (<22 days) compared with delayed (22–56 days) TTC (HR for death 0.84, 95%CI 0.67–1.06). Once results were adjusted for the presence of residual disease, TTC was no longer associated with progression free survival (HR for death 0.99, 95%CI 0.79–1.24).

A third meta-analysis included results from two studies ($n = 362$).⁶⁹ The trial populations included patients with stage II–IV ovarian cancer with no restriction on age (range: 22–78 years). Pooled data for the TTC analysis was adjusted for trial effects to remove the influence of either interventional study; no significant differences between the trials were identified ($p = 0.64$). Again, this represents level III evidence as patients were not randomised according to TTC. TTC was evaluated above and below the cut-off of 21 days (rationale unclear). The median and range of TTC were not reported making it difficult to define the representativeness of the TTC cohorts. Univariate analysis indicated increased risk of death with TTC >21 days vs ≤ 21 days (HR for death 1.33, 95%CI 1.05–1.68). However as with the previous

study, once adjusted for known prognostic indicators including the presence of residual disease, the relationship between TTC and survival was no longer significant.

Six of the seven retrospective series evaluating TTC of varying intervals demonstrated no survival difference when initiating chemotherapy up to 6 weeks post-surgery.⁷⁰⁻⁷⁵ The median TTC within these studies ranged from 21–42 days. The single retrospective study demonstrating an increased risk of death with TTC >28 days (compared with <28 days) demonstrated significance only for patients with residual disease.⁷⁶ This result contrasts with that from the earlier described meta-analysis which demonstrated significance only for patients with no residual disease.⁶⁷ Explanation for this contrary finding is yet to be determined.

Although excluded from this review the publications by Wright and colleagues are worthy of brief discussion given that they include the largest study population of any of the included studies (n=3991 in the 2012 study).^{77, 78} These studies were excluded because while adjusting for known prognostic factors of stage, surgical complications and comorbidities, they did not adjust for residual disease status. This limitation was noted by the authors in the first of the publications⁷⁷ and explained by the fact that the registry database from which data was retrospectively extracted (National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry) does not include information relating to residual tumour volume. Generally, patients with residual disease have earlier TTC and have worse outcomes.⁷⁹ The combined effect of which mean that results from this study would be biased toward negative outcomes for early TTC, and to that any detrimental effects of delayed TTC may be masked. The results of this study were therefore considered to contain unreasonable uncertainty and not appropriate for inclusion when forming recommendations for clinical practice. Nonetheless, for completeness, results are described briefly. Focussing on the second study (which includes data from the first), TTC was evaluated for intervals of less than 6 weeks, 6–12 weeks and more than 12 weeks post-surgery.⁷⁸ Compared with patients with TTC within 6 weeks of surgery, no impact on overall survival was demonstrated for delay in treatment initiation of up to 12 weeks; However, delay of more than 12 weeks was associated with increased risk of death (HR for death 1.32, 95%CI 1.07–1.64). Whilst 24% (n = 838) of patients in this study initiated chemotherapy between 6–12 weeks, only 4.2% (n = 147) initiated chemotherapy beyond 12 weeks limiting the ability to draw any conclusions about this population due to the effects of individuals being likely to impact on overall results.

Implications for practice

The optimal timing of chemotherapy in ovarian cancer remains unclear. In the two studies demonstrating an association between delayed TTC (at TTC >1 or >4 weeks) and reduced overall survival, conflicting results were reported for the influence of residual disease.^{67, 76} While a minority of studies were able to demonstrate negative effects of delayed TTC, the overall low evidence level warrants cautious interpretation of findings. With no foreseeable risk of early chemotherapy initiation and with a possibility of reduced survival outcomes due to delays, based on conservative interpretation of best available but low level evidence, it is suggested that chemotherapy should be initiated within 1–

4 weeks of surgery (level III, grade C). For the purposes of implementing local health policy and a desire for a single time point from which to monitor performance, it is reasonable to apply the longer range (treat within 4 weeks), due to the numerous negative studies showing no survival impact out to and beyond this time. Although the evidence is unclear, TTC may be more urgent for those with residual disease, and for these patients treatment should commence as soon as possible. Without direct scientific evidence, it is recommended that timely initiation of chemotherapy in patients not planned for initial surgery reflects that of post-surgery chemotherapy and commence within 4 weeks. Consistent recommendations for timely initiation of treatment in both surgical and non-surgical settings are also considered advantageous for the purposes of providing a standardised care to all patients. The recommended 4 week TTC interval also reflects recommendations included in newly drafted Australian clinical practice guidelines.⁹

Limitations:

It is a noted limitation that the applied search strategy within this systematic review was restricted to just two databases. This may have introduced bias into the results by omitting studies published in journals not indexed in these specific databases. Review of reference lists of relevant studies and search of grey literature aimed to minimise this risk through identification of papers indexed elsewhere. Limiting the search to two databases was a pragmatic decision based on resource allocation.

The strength of the recommendations provided by this review are limited to the strength of available evidence which varied from very strong (level I) to absence of evidence. Inclusion of heterogeneous patient cohorts and varied chemotherapy regimens also contributed to uncertainty.

Despite more relaxed eligibility criteria compared with reviews conducted in solid cancers, (allowing inclusion of abstracts and not specifying adjustment or stratification for known prognostic factors), there was an overall paucity of relevant studies evaluating the impact of TTC for lymphoma and myeloma.

Conclusions:

Breast Cancer:

The optimal timing of chemotherapy in breast cancer is unclear. Available studies are of low quality, report inconsistent results, and are limited to the adjuvant setting. Increased TTC may have a negative prognostic impact and based on conservative interpretation of level III evidence, delays beyond 4 weeks should be avoided.

Colorectal cancer:

Studies suggest that the optimal timing for initiation of adjuvant chemotherapy for surgically resected colorectal cancer is between 4 and 8 weeks post-surgery. Timing of chemotherapy for metastatic colorectal cancer not been shown to influence survival. Evidence in the neoadjuvant setting is lacking.

Lymphoma and Myeloma:

There is a paucity of studies to guide the timing of chemotherapy for the treatment of lymphoma and myeloma. For all cases, TTC should be guided by the treating haematologist with immediate treatment for all urgent presenting lymphoma or myeloma, with commencement within four weeks for intermediate to high-grade lymphoma and symptomatic myeloma and a shared patient and clinician agreement regarding timeliness of treatment for asymptomatic or indolent disease.

Lung cancer:

The optimal timing of chemotherapy in lung cancer is unclear; however, rapid tumour growth and poor disease prognosis suggest that delays should be avoided wherever possible. This is likely to be of greatest importance for curative intent treatments where delays may result in conversion from a curable to incurable disease state with significantly poorer prognoses for patients receiving palliative compared to curative intent treatment. The optimal timing for initiation of adjuvant chemotherapy for surgically resected NSCLC is not well defined and practice may best be guided by the original adjuvant study protocols which commence chemotherapy within 8 weeks of surgery. Definitive or palliative chemotherapy for inoperable NSCLC is likely to prevent disease progression and preserve treatment options if commenced within three weeks. Chemotherapy for SCLC should commence immediately due to high early doubling time and poor prognosis. Current practice suggests that SCLC patients should wait no longer than 2 weeks to commence chemotherapy.

Ovarian cancer:

The optimal timing of chemotherapy in ovarian cancer is unclear as available studies are of low level, report inconsistent results, and are limited to the post surgery setting; however, increased TTC may have a negative prognostic impact and based on conservative interpretation of level III evidence, delays beyond 4 weeks should be avoided.

TTC has not been a priority research area; however, increasing demand for cancer treatment may increase this interval. Understanding its importance is crucial to ensure that health-services provide care in a timeliness that maximises patient outcomes. Guidelines for the timely initiation of chemotherapy that have been informed by this systematic literature review are now available (Timely initiation of chemotherapy. Part 1: a proposed framework for access to medical oncology and haematology cancer clinics and chemotherapy services) [insert citation].

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Conflict of Interest:

These guidelines were produced independently by members of the project writing group. No conflicts of interest are declared.

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Table 1

Grades and levels of evidence according to the National Health and Medical Research Council of Australia (NHMRC) and the Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomized studies.^{12, 13}

Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
Level	Description
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls (non-randomised experimental trial, cohort study, case-control study, interrupted time series with a control group)
III-3	A comparative study without concurrent controls (historical control study, two or more single arm study, interrupted time series without a parallel control group)
IV	Case series with either post-test or pre-test/post-test outcomes
Quality Rating	Description
Maximum 4 points	Selection Criteria – representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, demonstration that outcome was not present at start of study.
Maximum 2 points	Comparability – Comparability of cohorts on basis of design and/or analysis.
Maximum 3 points	Outcome – assessment of outcome, follow-up time, adequacy of follow-up of cohorts.

Table 2

Summary of included studies for breast cancer – sample size, demographics, outcome measures, follow-up time and quality rating

Study	Sample size	Stage / Grade	Age	Outcome Measure	Follow-up median (range)	Level of Evidence [†]	Quality Score [‡]
de Melo Gagliato 2014 ¹⁴	6,827	stage I-II: 84.5%; stage III: 15.5%	Median: 50 Range: 19–85	OS, RFS, DFS	59.3 months (NR)	III-2	8
Downing 2014 ¹⁵	Region 1: 6,100	Stage I: 16.2%; stage II: 73.5%; stage III: 10.3%	Mean: 50.5 SD: 9.6	OS	NR (NR)	III-2	5
	Region 2: 4,266	stage I: 17.7% ; stage II: 70.9%; stage III: 11.4%	Mean: 51.1 SD: 9.9				
Yu 2013 ²²	34,097	stage I-III: 100%	NR	OS, DFS	NR (NR)	III-2	7
Alkis 2011 ¹⁶	402	grade I: 5.4%; grade II: 36.5%; grade III: 21.1%; unknown: 36.8%	Median: 47 Range: 24–80	OS, DFS	50 months (6-105)	III-2	8
Jara Sanchez 2007 ¹⁷	2,782	stage I: 15.1%; stage II: 70.1%; stage III: 14.0%	Median: 52 Range: 25-93	OS, DFS	72 months (NR)	III-2	8
Shannon 2003 ¹⁸	1,161	grade 1: 4.6%; grade 2: 40.1%; grade 3: 51.0%; unknown: 3.5%	Median: 48 Range: 18–75	DFS, OS	39 months (12–147)	III-2	7
Samur 2002 ¹⁹	96	stage I-II: 57.3%; stage III: 30.2%	Median: 43 Range: NR	RFS	9 years (NR)	III-2	6
Buzdar 1982 ²⁰	460	stage II: 63%; stage III: 22.4%; stage IV: 14.6%	<50: 48.3%	DFS	49 months (NR)	III-2	8

Study [†]	Sample size	Stage / Grade	Age	Outcome Measure	Follow-up median (range)	Level of Evidence [†]	Quality Score [‡]
Ahmann 1982 ²¹	77	advanced stage; 100%	Median: 44.5	OS, PFS	NR (>4 years)	II	9

†National Health and Medical Research Council Grades and Levels of Evidence;⁶⁰ ‡Newcastle Ottawa Quality rating for observational studies;¹³ DFS: disease free survival; NR: not reported; OS: overall survival; PFS: progression free survival; RFS: relapse free survival

Table 3

Summary of included studies for breast cancer – time-to-chemotherapy (TTC) interval and cohort and summary findings

Study	TTC interval	TTC Cohorts	Association TTC and survival	Summary Finding
de Melo Gagliato 2014 ¹⁴	Surgery to CHT	≤30 days, 31–60 days, ≥61 days	Yes†	Entire cohort: No difference overall survival by TTC (p=0.54) Stage III disease: TTC ≥61 days vs ≤30 days (HR for death 1.76, 95%CI 1.26–2.46, p < 0.001) HR+ disease: TTC ≥61 days vs ≤30 days (HR for death 1.29, 95%CI 1.02–1.64, p = 0.03) HER2+ disease treated with trastuzumab: TTC ≥61 days vs ≤30 days (HR for death 3.09, 95%CI 1.49–6.39, p = 0.002) Triple negative disease: TTC 31–60 days vs ≤30 days (HR for death 1.74, 95%CI 1.32–2.29, p < 0.001)
Downing 2014 ¹⁵	Surgery to CHT	≤3 weeks, 3–6 weeks, 6–10 weeks, >10 weeks	Yes	Entire cohort: TTC >10 weeks vs ≤3 weeks (HR for death 1.49, 95%CI 1.13–1.95)
Yu 2013 ²²	Surgery to CHT	Per 4 weeks	Yes	Entire cohort: Per each 4 week delay (HR for death 1.15, 95%CI 1.03–1.28 and HR for recurrence 1.16, 95%CI 1.01–1.33)
Alkis 2011 ¹⁶	Surgery to CHT	<14 days, 14–29 days, 30–44 days, 45–59 days, ≥60 days, ≤44 days vs ≥45 days, ≤90 days vs >90 days	Yes	Entire cohort: TTC ≤44 days vs ≥45 days (5 year overall survival 92% vs 83.3%, p = 0.03). No difference in DFS by TTC (p > 0.05)
Jara Sanchez 2007 ¹⁷	Surgery to CHT	<3w weeks, 3–6 weeks, 6–9 weeks, ≥9 weeks	No (inverse)	Entire cohort: No differences OS or DFS by TTC (p > 0.1) ER negative disease: Increased DFS with increased TTC (66.0%; 73.4%; 61.8%, 78.2% for lowest to highest TTC interval, p = 0.0219)

Study	TTC interval	TTC Cohorts	Association TTC and survival	Summary Finding
				<p>>10 nodes: Increased 5-year OS with increased TTC (55.5%; 67.7%; 68.9%, 94.4% for lowest to highest TTC interval, $p = 0.0068$)</p> <p>Age <50: Variable effect of 5-year OS by TTC interval (86.5%; 92.2%; 90.2%, 89.7% for lowest to highest TTC interval, $p = 0.013$)</p> <p>CMF chemotherapy: Variable effect of 5-year OS by TTC interval (88.7%; 90.8%; 84.7%, 90.1% for lowest to highest TTC interval, $p = 0.0541$)</p>
Shannon 2003 ¹⁸	Surgery to CHT	<21days vs >21 days, <28d days vs >28d days, <35 days vs >35 days, per 1 day delay	No	Entire cohort: No differences OS or DFS by TTC cohorts ($p > 0.2$)
Samur 2002 ¹⁹	Diagnosis to CHT Surgery to CHT	<35 days vs ≥ 35 days, <43 days vs ≥ 43 days	No	<p>Entire cohort TTC from diagnosis date: no difference RFS by TTC ($p = 0.05$)</p> <p>Entire cohort TTC from surgery date: no difference RFS by TTC ($p = 0.42$)</p>
Buzdar 1982 ²⁰	Surgery to CHT	<10 weeks, 10–13 weeks, 14-17 weeks, ≥ 18 weeks	Yes [†]	<p>Entire cohort: No difference OS by TTC ($p = 0.39$)</p> <p>Patients with poor prognostic indicators: Reduced 4-year DFS with increased TTC (47%, 69%, 24%, 46% for lowest to highest TTC interval, $p = 0.01$)</p>
Ahmann 1982 ²¹	Surgery to CHT	<21d, ≥ 21 d	No	Entire cohort: No difference OS by TTC ($p=0.91$)

[†]significant effect demonstrated in subgroups only; CHT: chemotherapy; CI: confidence interval; CMF: cyclophosphamide methotrexate and fluorouracil; DFS: disease-free survival; ER: estrogen receptor; HR: hazard ratio; hormone receptor positive; HER2+: human epidermal growth factor receptor 2 positive; OS: overall survival

Table 4

Summary of included studies for colorectal cancer – sample size, demographics, outcome measures, follow-up time and quality rating

Study	Sample size	Population	Age	Outcome Measure	Follow-up Median (range)	Level of Evidence [†]	Quality Score [‡]
Day 2014 ³⁸	209	stage I & II: 84.5% stage III: 15.5%	Median: 50 Range 19–85	OS, RFS, DFS	Median: 30 months	III-2	8
Tevis 2013 ³⁷	355	Surgically resectable rectal cancer	Median: 60 Range: 29–95	OS	Median: 59.3 months	III-2	5
Kang 2013 ³⁶	159	Surgically resectable stage III colorectal cancer	Mean: 63.7 Range: 29–89	OS, RFS	Group 1 - Mean 41.5 months Group 2 – Mean 50.3 months Group 3 – Mean 47.4 months	III-2	5
Voskoboynik 2012 ³⁵	377	Metastatic colorectal cancer	Median: 67.9 Range: 26–96	OS	NR [§]	III-2	6
Biagi 2011 ³² Meta-analysis of 10 level III studies	15,410	Stage II-III colon or rectal cancers	NR	OS, DFS	NR	III-2	NA
Des Guetz. G. 2010 ³³ Meta-analysis of 8 level III studies	13,158	Stage II/III colon or rectal cancer	Median 57–73	OS, RFS	NR	III-2	NA
Ackland 2005 ³⁴ Meta-analysis two level II studies	84	Metastatic colorectal cancer	Median: 63–67 Range: 36–80	TTP, OS, QOL	55 months (NR)	I	NA

†National Health and Medical Research Council Grades and Levels of Evidence;⁶⁰ ‡Newcastle Ottawa Quality rating for observational studies;¹³ DFS: disease free survival; NA: not applicable; NR: not reported; OS: overall survival; QOL: quality of life; RFS: relapse free survival; TTP: time to progression

Table 5

Summary of included studies for colorectal cancer – time-to-chemotherapy (TTC) interval and cohort and summary findings

Study	TTC ¹ interval	TTC Cohorts	Association TTC and survival	Summary Finding
Day, 2014 ³⁸	Surgery to CHT	< 8 weeks vs ≥ 8 weeks	Yes	Increased risk of death with TTC >8 weeks compared to less than 8 weeks (5-year OS 89.6% and 73.5% with TTC <8 weeks and >8 weeks respectively, p = 0.016).
Tevis 2013 ³⁷	Surgery to CHT	<8 weeks, >8 weeks	Yes	Increased risk of death with TTC >8 weeks compared to less than 8 weeks (OR for death 3.123, 95% CI 1.605–6.078; p = 0.001)
Kang 2013 ³⁶	Surgery to CHT	<2 weeks, 3–4 weeks, >5 weeks	No	No difference in OS by TTC cohort (p = 0.37) No difference in RFS by TTC cohort (p = 0.41)
Voskoboynik 2012 ³⁵	Diagnosis to CHT	Immediate CHT vs watch & wait	No (inverse)	Reduced risk of death with delayed TTC (watch-and-wait) compared with immediate treatment (HR for death 0.68, 95% CI 0.54–0.85, p = 0.0008).
Biagi 2011 ³²	Surgery to CHT	Continuous variable	Yes	Increased risk of death per 4 week increase in TTC (HR for death 1.14, 95%CI 1.10–1.17). Increased risk of progression per four week increase in TTC (HR for progression 1.14, 95%CI 1.10–1.18).
Des Guetz 2010 ³³	Diagnosis to CHT	<8 weeks, >8 weeks	Yes	Increased risk of death with TTC >8 weeks compared with <8 weeks (HR for death 1.20, 95%CI 1.15–1.26). No difference in RFS by TTC cohort.
Ackland 2005 ³⁴	Surgery to CHT	Immediate CHT vs watch & wait	No	No difference in TTP with delayed TTC (watch-and-wait) compared with immediate treatment (HR for progression 1.08, 95%CI 0.71–1.64, p = 0.73). No difference in OS with delayed TTC (watch-and-wait) compared with immediate treatment (HR for death 1.15, 95%CI 0.77–1.72, p = 0.49). No difference in QOL with delayed TTC (watch-and-wait) compared with immediate treatment (QOL measured bimonthly for 2 years).

CHT: chemotherapy; CI: confidence interval; HR: hazard ratio; OR: odds ratio; OS: overall survival; RFS: relapse-free survival; TTP: time to progression

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Table 6

Summary of included studies for lymphoma

Study	Sample Size	Population	TTC Interval	Study Design	Outcomes	Summary Results	Level of Evidence [†]	Quality Score [‡]
Brooks 2013 ⁴¹	879	HL	Histological diagnosis to first chemotherapy	Retrospective Cohort Study (registry)	OS [/] , PFS ^{>}	5-year OS: 90% for TTC <2 weeks, 93% for 3–4 weeks, 92% for 5–8 weeks, 84% for >8 weeks (p = 0.012).	III-2	8
Nikonova 2013 ⁴⁰	278	DLBCL ¹	First haematology consult to first chemotherapy	Retrospective Cohort Study (single centre)	OS, PFS	Delays in DLBCL treatment of >1 month do not affect OS (significance not reported)	III-2	6

†National Health and Medical Research Council Grades and Levels of Evidence;⁶⁰ ‡Newcastle Ottawa Quality rating for observational studies;¹³ DLBCL: Diffuse Large B-Cell Lymphoma; HL: Hodgkin's Lymphoma; OS: overall survival; PFS: progression free survival; TTC: time to chemotherapy

Table 7

Summary of included studies for non-small cell lung cancer – sample size, demographics, outcome measures, follow-up time and quality rating

Study	Sample size	Stage	Histology	Performance Status	Age	Outcome Measure	Follow-up Median (range)	Level of Evidence [†]	Quality Score [‡]
Booth 2013 ⁵⁵	1,032	I: 14%, II: 8%, III: 38%, IV: 40%	Adeno: 54% Squamous: 29% Other: 17%	Charlson Index§ 0: 80%, 1–2: 18%, ≥3: 2%	Median: 62 Range: 28–85	OS	NR (NR)	III-2	7
Diaconescu 2011 ⁵²	319	NR	Squamous: 23% Other: 77%	NR	Median: 62 Range: 26–82	OS	8 months (NR)	III-2	7
Everitt 2013 ⁴⁹	21	I: 7%, II: 9%, III: 76%, IV: 0%	Adeno: 33% Squamous: 48% Other: 19%	NR	Median: 68 Range: 45–87	OS, PFS, Tumour Growth	29 months (13–37)	III-2	7
Loh 2006 ⁵³	122	I-II: 5%, III: 86%, IV: 9%	Adeno: 46% Squamous: 30% Other: 24%	NR	<55: 25% 55–70: 50% >70y: 25%	OS	NR (NR)	III-2	7
Mydral 2004 ⁵⁴	466	I-II: 31%, IIA: 8%, IIIB: 34%, IV: 28%	Adeno: 42% Squamous: 32% Other: 26%	NR	Median: NR Range: 39–89	OS	20 months (0–85)	III-2	7
O'Rourke 2000 ⁵⁰	29	NR	Adeno: 24% Squamous: 69% Other: 7%	NR	Median: 67 Range: 45–83	Tumour Growth	NA	III-2	7
Radzikowska 2012 ⁵⁹	10,583	I: 2%, II: 14%, III: 42%, IV: 16%	NR	ECOG PS¶ 0–1: 58%, 2: 31%, 3–4: 11%	<50y: 13% >50y: 87%	OS	NR (NR)	III-2	7

Study	Sample size	Stage	Histology	Performance Status	Age	Outcome Measure	Follow-up Median (range)	Level of Evidence [†]	Quality Score [‡]
Wang 2009 ⁵¹	237	III: 100%	Adeno: 33% Squamous: 29% Other: 38%	Karnofsky PS [§] Median: 2, Range: 0–10, >2: 36%	Median: 65 Range: 34–89	OS	5.8 years (NR)	III-2	7

†National Health and Medical Research Council Grades and Levels of Evidence;⁶⁰ ‡Newcastle Ottawa Quality rating for observational studies;¹³ §Charlson Comorbidity Index; ¶eastern cooperative oncology group performance status; §Karnofsky performance status; Adeno: adenocarcinoma; NA: not applicable; NR: not reported; OS: overall survival; PFS: progression free survival; Squamous: squamous cell carcinoma

Table 8

Summary of included studies for small-cell lung cancer (SCLC) – sample size, demographics, outcome measures, follow-up time and quality rating

Study	Sample size	Stage	Histology	Performance Status	Age	Outcome Measure	Follow-up Median (range)	Level of Evidence [†]	Quality Score [‡]
Berthelet 2006 ⁵⁶	166	Limited: 100%	NA	NR	Median: 68 Range: 35–86	OS, CSS, CR, TR	52m (10–92m)	III-2	8
Haque 2012 ⁵⁸	45	Limited: 39% Extensive: 61%	NA	NR	Median: 69 Range: 45–88	OS	3.3y (1.8–6.2y)	III-2	7
Radzikowska 2013 ⁵⁷	3,479	Limited: 32% Extensive: 68%	NA	ECOG PS§ 0–1: 12%, 2: 32%, 3–4: 56%	Mean: 60 Standard Deviation: 10	OS	NR (NR)	III-2	7

†National Health and Medical Research Council Grades and Levels of Evidence;⁶⁰ ‡Newcastle Ottawa Quality rating for observational studies;¹³ §eastern cooperative oncology group performance status; CR: complete response; CSS: cancer specific survival; NA: not applicable; NR: not reported; OS: overall survival; TR: thoracic response

Table 9

Summary of included studies for non-small-cell lung cancer – time-to-chemotherapy (TTC) interval and cohort and summary findings

Study	TTC interval	TTC Cohorts	CHT	Association TTC and survival	Summary Finding
Booth 2013 ⁵⁵	Surgery to CHT	≤10 weeks >10 weeks, per day	NR	No	Entire cohort: No survival impact of delayed TTC (HR for death per day delay 1.00, 95%CI 0.99–1.00, p = 0.786)
Diaconescu 2011 ⁵²	Abnormal radiograph to First Treatment [†]	per day	Platinum based	No (inverse)	Local/regional disease: No survival impact of delayed TTC (HR not reported) Stage IIIB-IV disease: Increased survival with delayed TTC (HR for death per 1 week and 1 month TTC 0.93, 95%CI 0.88–0.98 and 0.74, 95%CI 0.59–0.93 respectively). Median OS with TTC ≤50 days vs >50 days: 7 vs 12 months (p = 0.027).
Everitt 2013 ⁴⁹	2 pre-treatment PET-CT scans	NA Median: 22 days Range (9–65)	NA	Yes	Entire cohort: Increased median tumour volume between scans: 105 vs 198 (p < 0.005). 29% (6/21) of patients converted from planned radical treatment to palliative treatment. Reduced risk of death with radical vs palliative RT (HR for death: 0.116, 95%CI 0.025–0.527, p < 0.001).
Loh 2006 ⁵³	First doctor (hospital) to first treatment [‡]	<30 days, 30–60 days, >60 days	NR	No	Entire cohort: No survival impact of delayed TTC (p = 0.577)
Mydral 2004 ⁵⁴	First doctor (hospital) to first treatment [§]	<1 month, 1–2 months, 2–3 months, >3 months, per month	NR	No	Entire cohort: No survival impact of delayed TTC (p > 0.6)

Study	TTC interval	TTC Cohorts	CHT	Association TTC and survival	Summary Finding
	First symptom to first treatment [§]	<3 months, 3–6 months, >6 months, per month		No	Entire cohort: No survival impact of delayed TTC (p > 0.7)
O'Rourke 2000 ⁵⁰	2 pre-treatment PET-CT scans	NA Median: 54 days Range: 18–131 days	NA	Trend	Entire cohort: Non-significant trend for association with delay and increased tumour growth (p = 0.06). >50% tumour growth in 6/29 patients and 20–50% tumour growth in another 6/29 patients. 6/29 pts (21%) with potentially curable disease, became incurable whilst waiting for treatment.
Radzikowska 2012 ⁵⁹	First Doctor (any) to first treatment [¶]	<42 days, >42days	NR	No (inverse)	Entire cohort: Increased risk of death with TTC <42 days vs >42days (HR for death 1.14, p = 0.001)
Wang 2009 ⁵¹	Radiological diagnosis to first treatment [§]	≤60 days, 61–90 days, >90 days	Combinations of carboplatin, etoposide, paclitaxel, cisplatin and vinorelbine	Yes¥	Patients with OS ≥5 years: Increased risk of death with TTC >90 days (HR for death 1.029, 95%CI 1.003–1.005, p = 0.029) Patients with OS ≥2 years: No difference in survival by TTC (p = 0.319) Patients with OS ≥3 years: No difference in survival by TTC (p = 0.207)

† percentage receiving chemotherapy as first treatment not reported, ‡69% either chemotherapy, chemo-radiotherapy or radiotherapy as first line treatment (not further defined), §46% received chemotherapy as first line treatment, ¶24% received chemotherapy as first line treatment, § 55% received chemotherapy as first line treatment; ¥ significant effect demonstrated in subgroups only; CHT: chemotherapy; CI: confidence interval; HR: hazard ratio; NA: not applicable; NR: not reported; OS: overall survival; PET-CT: positron emission tomography-computed; RT: radiotherapy;.

Table 10

Summary of included studies for small-cell lung cancer – time-to-chemotherapy (TTC) interval and cohort and summary findings

Study	TTC interval	TTC Cohorts	CHT	Association TTC and survival	Summary Finding
Berthelet 2006 ⁵⁶	First doctor (oncologist) to CHT	≤15 days, >15 days	CAV/EP or oral etoposide alone if elderly or frail	No	Entire cohort: No survival impact of delayed TTC (p > 0.3)
Haque 2012 ⁵⁸	Abnormal radiograph to CHT	A: median TTC 15 days B: median TTC 39 days	NR	No	Entire cohort: No survival impact of delayed TTC (p non-significant but actual value NR)
Radzikowska 2013 ⁵⁷	First doctor (any) to CHT	<42 days, >42 days	NR	No (inverse)	Entire cohort: Increased risk of death with TTC <42 days vs >42 days (HR for death 1.20, p = 0.002)

CAV/EP: Cyclophosphamide, doxorubicin and vincristine or etoposide; CHT: chemotherapy; HR: hazard ratio; NR: not reported

Table 11

Summary of included studies for ovarian cancer – sample size, demographics, outcome measures, follow-up time and quality rating

Study	Sample size	Stage / Grade	Age	Outcome Measure	Follow-up Median (range)	Level of Evidence [†]	Quality Score [‡]
Lydisken 2014 ⁷²	327	Any stage	Median: 63.1	OS	82.1 months (NR)	III-2	9
Hofsetter, 2013 ⁷⁶	191	Stage III–IV	Group 1: 60 Group 2: 61	OS	3.5 years (4–69 months)	III-2	7
Mahner, 2013 ⁶⁷ Meta-analysis of 3 RCTs	3326	Stage IIB–IIIB 26%; Stage IIIC 57%; Stage IV 17%	Median: 60 Range: 19–83	OS, PFS	52.8 months	III-2	NA
Aletti, 2007 ⁷⁰	218	Stage IIIC or IV	Mean: 64	OS, DFS	Minimum 5 years	III-2	7
Paulsen, 2006 ⁷³	213	Advanced	>65	OS	22 months (13 days–39 months)	III-2	7
Rosa, 2006 ⁷⁴	394	Advanced	Median: 62 Range: 12–85	OS	19 months (NR)	III-2	7
Gadducci, 2005 ⁷¹	313	Stage IIC 7.7%; Stage III 79.6%; Stage IV 12.8%	Median: 56 Range: 23–77	OS, RR	30.7 months	III-2	8
Sorbe, 2004 ⁷⁵	1120	Stage I 39.7%; Stage II 12.8%; Stage III 29.4%; Stage IV 18.1%	NR	OS	9.8 years (5–20 years)	III-2	9
Flynn, 2002 ⁶⁸ Meta-analysis of 4 RCTs	427	Stage IIB–IV 100%	NR	PFS	3.5 years (2–10 years)	III-2	NA
Warwick, 1995 ⁶⁹ Meta-analysis of 2 RCTs	362	Stage II 7%; Stage III 75%; Stage IV 18%	NR	OS	6.5 years	III-2	NA

†National Health and Medical Research Council Grades and Levels of Evidence;⁶⁰ ‡Newcastle Ottawa Quality rating for observational studies;¹³ DFS: disease free survival; NR: not reported; OS: overall survival; PFS: progression free survival; RCT: randomised controlled trials; RR: response rate

Table 12

Summary of included studies for ovarian cancer – time-to-chemotherapy (TTC) interval and cohort and summary findings

Study	TTC interval	TTC Cohorts	Association TTC and survival	Summary Finding
Lydisken 2014 ⁷²	Surgery to CHT	≤32 days, ≥32 days	No	No difference in OS with TTC >32 days compared with <32 days (HR for death 1.13, 95% CI 0.92–1.39, p = 0.26)
Hofsetter, 2013 ⁷⁶	Surgery to CHT	Patients with RD ≤28 days, >28 days	Yes	Increased risk of death with TTC >28 days compared with <28 days (HR for death 2.24, 95% CI 1.08–4.66, p = 0.031)
		Patients without RD ≤28 days, >28 days	No	No difference in OS by TTC cohort (HR NR)
Mahner, 2013 ⁶⁷ Meta-analysis of 3 RCTs	Surgery to CHT	Patients with RD Per week delay	No	No difference in OS per week delay (HR 0.938, 95% CI 0.94–1.028, p = 0.452)
		Patients without RD Per week delay	Yes	Increased risk of death per week delay (HR 1.087, 95% CI: 1.005–1.176, p = 0.038)
Aletti, 2007 ⁷⁰	Surgery to CHT	All patients: ≤17 days, 18–26 days, 27–33 days, ≥34 days	No	No difference in OS by TTC cohort; (OR for death 1.00, 95% CI 0.98–1.01, p = 0.85)
		Patients with RD <1cm: ≤17 days, 18–26 days, 27–33 days, ≥34 days	No	No difference in OS by TTC cohort; p = 0.93
		Patients with RD >1cm: ≤17 days, 18–26 days, 27–33 days, ≥34 days	No	No difference in OS by TTC cohort; p = 0.51
Paulsen, 2006 ⁷³	Surgery to CHT	All patients: 0–14 days, 15–29 days, 30–39 days, >40 days	No	No differences OS or by TTC cohorts; p = 1.0
		Patients with RD: <6 weeks, >6 weeks	NR	Outcome NR; reported HR for patients with RD compared with those without RD and the same TTC interval (HR for death 2.36, 95% CI, 1.22–4.57).

Study	TTC interval	TTC Cohorts	Association TTC and survival	Summary Finding
		Patients without RD: <6 weeks, >6 weeks		
Rosa, 2006 ⁷⁴	Surgery to CHT	<4 weeks, >4 weeks	No	Non-significant trend for worse survival with TTC >6 weeks compared with <6 weeks (HR for death 1.35; 95% CI, 0.51–3.56)
Gadducci, 2005 ⁷¹	Surgery to CHT	<11 days, 12–21 days, 22–31 days, >31 days	No	No differences in OS by TTC cohort (p = 0.1091)
Sorbe, 2004 ⁷⁵	Surgery to CHT	Per day delay	No	No differences in OS by TTC cohort (HR for death per day delay 0.998, 95% CI 0.991–1.006, p = 0.647)
Flynn, 2002 ⁶⁸ Meta-analysis of 4 RCT	Surgery to CHT	<22 days, 22–56 days	No	No difference in PFS with TTC 22–56 days compared with <22 days (HR for death 0.99, 95% CI 0.79–1.25, p = 0.91).
Warwick, 1995 ⁶⁹ Meta-analysis of 2 RCT	Surgery to CHT	≤ 21days, >21 days	No	No difference in OS by TTC cohort (p > 0.05)

CHT: chemotherapy; CI: confidence interval; HR: hazard ratio; NR: not report; OR: odds ratio; OS: overall survival; PFS: progression free survival; RCT: randomised controlled trials; RD: residual disease;

ABSTRACT:

This review evaluated the association between time-to-chemotherapy (TTC) and survival in six priority cancers. A systematic review of the literature was undertaken for papers indexed in MEDLINE and Cochrane Library databases from earliest index until April 2014. The methodology used has been published in a separate paper (Timely initiation of chemotherapy. Part 1: a proposed framework for access to medical oncology and haematology cancer clinics and chemotherapy services). The optimal timing of chemotherapy in breast cancer is unclear as available studies are of low quality, report inconsistent results, and are limited to the adjuvant setting. However, increased TTC may have a negative prognostic impact and delays beyond 4 weeks should be avoided. Studies suggest that the optimal timing for initiation of adjuvant chemotherapy for surgically resected colorectal cancer is 4–8 weeks post-surgery. Timing of chemotherapy for metastatic colorectal cancer does not influence survival. There is a paucity of studies to guide the timing of chemotherapy for the treatment of lymphoma and myeloma; no definitive conclusions can be drawn and clinician discretion should be applied. The optimal timing of chemotherapy in lung cancer is unclear; however, rapid tumour growth and poor disease prognosis suggest that delays should be avoided wherever possible. The optimal timing of chemotherapy in ovarian cancer is unclear as available studies are of low level, report inconsistent results, and are limited to the post surgery setting; however, increased TTC may have a negative prognostic impact, therefore; delays beyond 4 weeks should be avoided.

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