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The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials

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Background: The granulocyte colony-stimulating factor (G-CSF) is utilized to reduce neutropenic complications in patients receiving cancer chemotherapy. This study represents a systematic review and evidence summary of the impact of G-CSF support on chemotherapy dose intensity and overall mortality.
Materials and methods: All randomized controlled trials (RCTs) comparing chemotherapy with or without G-CSF support and reporting all-cause mortality with at least 2 years of follow-up were sought. Dual-blind data abstraction of disease, treatment, patient and outcome study results with conflict resolution by third party was carried out.
Results: The search revealed 61 randomized comparisons of chemotherapy with or without initial G-CSF support. Death was reported in 4251 patients randomized to G-CSFs and in 5188 controls. Relative risk (RR) with G-CSF support for all-cause mortality was 0.93 (95% confidence interval: 0.90–0.96; $P < 0.001$). RR for mortality varied by intended chemotherapy dose and schedule: same dose and schedule (RR = 0.96; $P = 0.060$), dose dense (RR = 0.89; $P < 0.001$), dose escalation (RR = 0.92; $P = 0.019$) and drug substitution or addition (RR = 0.94; $P = 0.003$). Greater RR reduction was observed among studies with longer follow-up ($P = 0.02$), where treatment was for curative intent (RR = 0.91; $P < 0.001$), and where survival was the primary outcome (RR = 0.91; $P < 0.001$).
Conclusions: All-cause mortality is reduced in patients receiving chemotherapy with primary G-CSF support. The greatest impact was observed in RCTs in patients receiving dose-dense schedules.
Key words: granulocyte colony-stimulating factors, neutropenia, survival

introduction

Clinical practice guidelines recommend the use of the myeloid growth factors for reducing the risk of neutropenic complications in high-risk patients receiving cancer chemotherapy as well as enabling delivery of full dose chemotherapy when that is considered important to control of the underlying malignancy and improve clinical outcomes [1–3]. Randomized controlled trials (RCTs) of recombinant granulocyte colony-stimulating factors (G-CSFs) have demonstrated significant reductions in the severity and duration of neutropenic complications while sustaining or increasing chemotherapy dose intensity [4]. Although meta-analyses of RCTs of G-CSFs administered as primary prophylaxis for febrile neutropenia (FN) have reported significant reductions in short-term all-cause as well as infection-related mortality [4], the impact of the myeloid growth factors on subsequent disease recurrence and overall survival continues to be debated.

Supportive care with the myeloid growth factors may improve chemotherapy delivery by minimizing chemotherapy dose reductions or treatment delays, by enabling the delivery of full-dose chemotherapy in short-time intervals (dose dense), by enabling an increase in chemotherapy dose on the same schedule (dose escalation) or by enabling the substitution or addition of another myelosuppressive drug to a standard regimen (drug addition). Although G-CSF may enable the safe delivery of these different approaches to sustaining or increasing chemotherapy dose intensity, the potential clinical impact on the disease and outcomes may be quite different. A recent review of studies reporting rates of second malignancies identified 25 RCTs comparing cancer chemotherapy with or without primary G-CSF support observed a significant increase in risk of acute myeloid leukemia and myelodysplastic syndrome along with a significant reduction in overall all-cause mortality favoring patients randomized to receive G-CSF

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support [5]. The current study was undertaken to identify all RCTs of patients receiving cancer chemotherapy comparing initial G-CSF support with controls and reporting overall survival with at least 2 years of follow-up.

methods

data source and search

A systematic literature review of RCTs and meta-analyses of RCTs of G-CSF in adult patients receiving chemotherapy was conducted for studies published between January 1990 and August 2009. This search was updated to August 2012 as discussed in the supplemental material, available at *Annals of Oncology* online. As shown in Figure 1, searched electronic databases included Medline, the Cochrane Library and conference proceedings from the American Society of Clinical Oncology and the American Society of Hematology. References of all identified eligible articles were hand searched for other relevant citations. Abstracts were selected for further evaluation if they represented randomized clinical trials of the G-CSF with concurrent placebo or non-placebo controls in cancer patients receiving systemic chemotherapy.

study selection

Eligible studies represented cancer patients receiving conventional dose chemotherapy for solid tumors or malignant lymphoma and randomized to primary G-CSF support in one arm versus a control group without initial G-CSF. Control subjects may have received no G-CSFs, G-CSFs at the discretion of the treating physician or secondary use of G-CSFs following the initial cycle of treatment. Therefore, there was no restriction on subsequent G-CSF use after cycle 1 in the control arm of studies based on cross-over designs or secondary use. Eligible studies were required to report overall survival or all-cause mortality by treatment group and report the follow-up of at least 24 months. Exclusion criteria included studies without randomization to G-CSF versus control without initial G-CSF, initial G-CSF given in all study arms, studies of granulocyte-macrophage CSF, studies of stem cell or bone marrow transplantation, studies of patients with a diagnosis of leukemia, studies where the chemotherapy regimens in the trial arms differed by more than one agent and other study types including review articles and economic analyses. When multiple publications about a study were identified, only those representing the most recent reference reporting the desired outcomes were included.

data extraction and quality assessment

Data were abstracted from all eligible sources by two independent reviewers using an a priori developed and approved data extraction form with a third reviewer resolving discordant results. Four groups of study designs related to delivered dose and schedule considered a priori in the data analysis plan included: (Group 1) patients planned to receive identical regimens (drugs, doses and schedule) in each arm of the study with the exception of G-CSF administration initially in one arm, (Group 2) patients randomized to dose-dense chemotherapy given at a shorter interval but the same total dose of drugs with G-CSF support versus a control regimen consisting of the same drugs and doses but at less frequent intervals, (Group 3) patients randomized to a dose-escalated regimen with G-CSF support in order to increase the dose of one or more of the same chemotherapy drugs generally given in the same interval but at higher doses and often to a greater cumulative dose versus a control regimen of the same drugs and schedule but lower doses of drug and (Group 4) patients randomized to a conventional or standard regimen versus the same regimen but with the substitution or addition of, at most, one additional myelosuppressive agent thought to provide a more intensive combination with the addition of G-CSF support.

The primary analysis plan was based on the estimation of all-cause mortality within the four a priori defined dose–schedule study designs (Groups 1–4). Secondary analyses were based on all-cause mortality overall and with various disease and prognostic factor subgroups as well as planned and delivered chemotherapy relative dose intensity (RDI). RDI was defined as the ratio of the dose per unit time either planned or delivered divided by the dose per unit time considered standard for the regimen utilized in the control arm based on a previously presented literature search of clinical practice guidelines and phase III RCTs [5]. Treatment effect was summarized as the relative risk (RR) or the absolute risk difference (ARD) in G-CSF-supported chemotherapy versus control patients. For studies in which the treatment arms included the same agents, the planned and the delivered RDIs were defined as the ratio of the planned or the delivered dose intensity in patients randomized to G-CSF-supported chemotherapy to that in patients in the control arm receiving standard dose intensity. Although pooled results across all studies are presented, the primary preplanned analysis is to present results for the four distinct chemotherapy dose and schedule regimen strategies with and without G-CSF support. Quality appraisal of eligible studies subjected to data abstraction was based on the dual-blinded assessment of the following factors: (i) whether sample size estimation was presented, (ii) appropriate statistical methods for analyzing the primary outcome were described, (iii) whether the flow of patients through the study was adequately described and (iv) whether adverse events were objectively reported. Intention–to-treat (ITT) analysis with respect to the overall survival was captured and classified as (i) strict with all randomized patients analyzed, (ii) loose with limited exclusions permitted, (iii) no ITT analysis and (iv) unclear.

data synthesis and analysis

Heterogeneity was evaluated on the basis of Cochran's Q statistic and the Inconsistency Index (I^2). Cochran's Q represents the weighted sum of squared differences between individual study effects and the pooled effect across studies [6]. I^2 is defined as:

$$100\% \times \frac{Q - \mathrm{df}}{Q},$$

where df is the degrees of freedom and can be thought of as the proportion of variation across studies due to heterogeneity rather than chance [7]. Significant heterogeneity was observed in the estimation of the RR but not the ARD for all-cause mortality. Random effects models where the effect in each trial

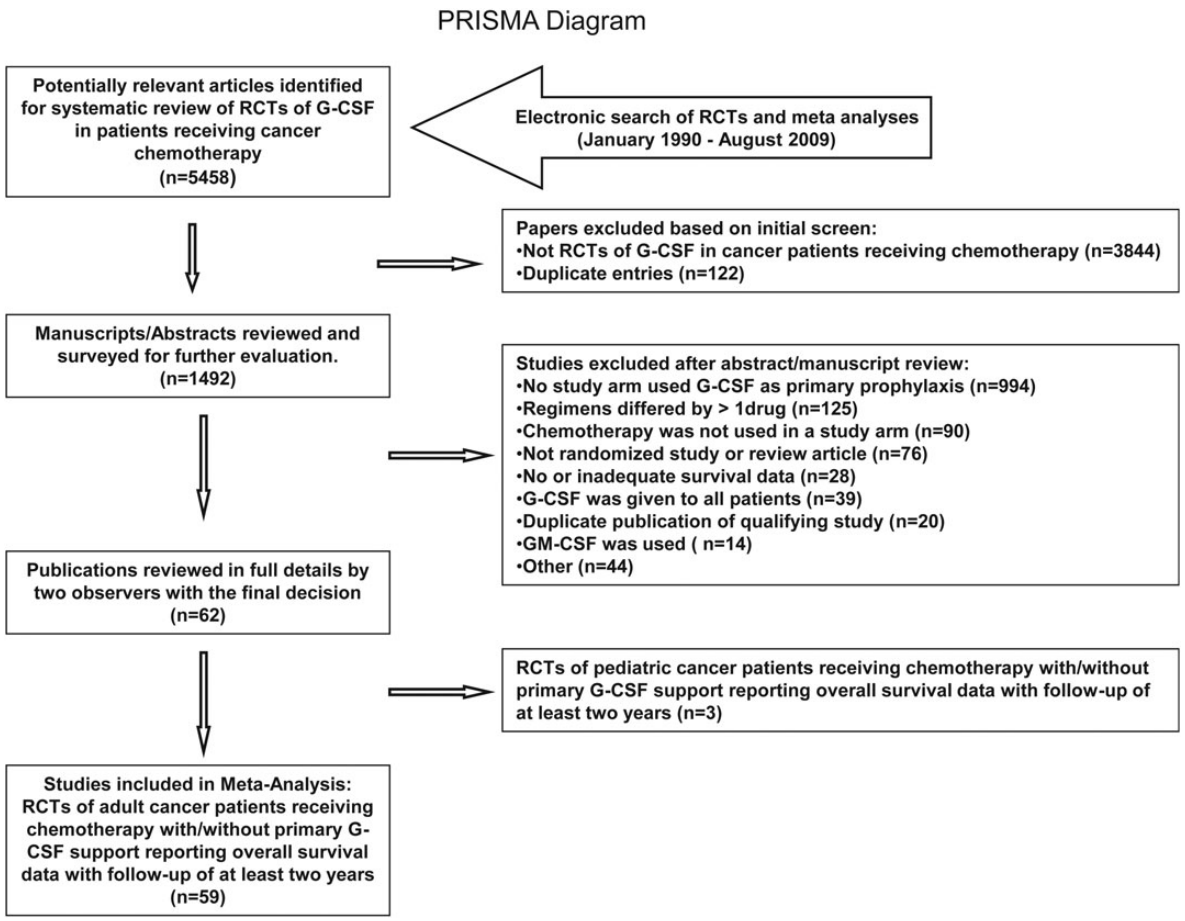

Figure 1. PRISMA diagram of RCTs of G-CSF-supported chemotherapy versus control for the study search and selection process. Review of each reference immediately excluded 3966 articles, whereas the remaining 1492 articles were subjected to a more detailed review of either the abstract or the full manuscript with the reasons for exclusion indicated in this figure. Outcomes were assessed in 61 separate randomized comparisons of chemotherapy with or without the initial use of G-CSFs.

is assumed to be a random sample from the underlying true distribution were utilized for summary estimates of the RR for mortality. The true treatment effect may differ between studies due to differences in outcome measures, patient populations or treatment variation between studies. Correlations between continuous measures were based on Kendall's tau or Spearman's rho statistics. Tests of linearity were based on the sum of squares, degrees of freedom and mean square associated with linear and non-linear components based on analysis of variance.

Summary effect estimates of the RR and ARD for mortality [95% confidence intervals (CIs)] were based on the method of Mantel and Haenszel using a random effects model as described by DerSimonian and Laird. Treatment assignment and a priori specified subgroups and study design parameters were formally evaluated for interaction by comparing the ratio of the difference in the natural logarithm of the RR and the standard error of the difference in log RR to the standard normal distribution. Summary estimation across trials was conducted using both RevMan 4 (Cochrane Collaboration, www.cochrane.org) and Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ, USA). Forest plots display the point estimates and 95% confidence limits for RR for each study along with weighted summary estimate across studies with weights inversely proportional to the estimate variance for each study. The area displayed for each point estimate of RR is based on the relative weight within subgroups based on the disease group. Planned and delivered chemotherapy RDIs with G-CSF support relative to control patients were regressed on the natural logarithm of the RR for mortality. Sensitivity analyses were carried out for a number of measures of study quality captured across included trials.

Publication bias was assessed qualitatively by the visual inspection of funnel plots of the relationship between the natural logarithm of the RR for mortality against the standard error of the difference for each outcome [8–10]. Funnel plot asymmetry was assessed quantitatively based on the rank correlation of Begg and Mazumdar with continuity correction and Egger's regression intercept method which utilizes the actual values of the effect sizes and their variance to regress the standardized effect on the inverse of the standard error [11, 12].

results

eligible studies

Figure 1 displays a PRISMA diagram for the study search and selection process. Review of each reference immediately

excluded 3966 articles. The remaining 1492 articles were subjected to a more detailed review of either the abstract or the full manuscript with the reasons for exclusion indicated in Figure 1. Of the 62 potentially eligible RCTs, three were in pediatric cancer patients and were also excluded from this analysis. The remaining 59 RCTs reporting overall survival with at least 2 years of follow-up provide the basis for this analysis. Due to the need to extract data from more than one publication source for several studies, a total of 72 publications served as the basis for data abstraction. Seven studies utilized a two by two factorial design of which two demonstrated significant interaction between the specific chemotherapy regimen and the G-CSF assignment [13, 14]. Outcomes were, therefore, assessed in 61 separate randomized comparisons of chemotherapy with or without the initial use of G-CSFs. Six studies included two control arms in a three arm study design [15–21]. The second control arm in two studies was not included as the chemotherapy regimen differed by two or more agents [18, 19]. In the other four studies, the results from the two control arms were combined and compared with the G-CSF-supported treatment arm in the summary analysis [15–17, 20, 21].

descriptive analysis

Among eligible studies, chemotherapy was administered with or without primary G-CSF support in 11 337 and 13 456 patients, respectively, with the median follow-up ranging from 7 to 188 months with the average median follow-up across studies of 37 months. Deaths occurred in 4251 patients randomized to receive G-CSFs compared with 5188 controls. Planned dose and schedule were the same in both arms (Group 1) in 15 trials ($N = 3890$), whereas G-CSF support was utilized with either dose-dense chemotherapy (Group 2) in 12 ($N = 6302$) or dose-escalated treatment (Group 3) in 18 ($N = 8520$). In 16 studies, primary G-CSF support was associated with the addition or substitution of a different agent (Group 4; $N = 6081$).

Among subgroups evaluated, cancer type among eligible trials included 20 with breast cancer ($N = 13\,836$; 56%), 16 lung cancer ($N = 3372$; 14%), 16 lymphoma ($N = 5488$; 22%), 7 genitourinary ($N = 1766$; 7.1%) and 2 other ($N = 331$; 1.3%). Patients were treated for curative intent in 26 studies ($N = 15\,995$; 65%) and non-curative in 35 ($N = 8798$; 35%), whereas survival was the primary study outcome in 37 studies ($N = 18\,943$; 76%) and a secondary outcome in 24 ($N = 5850$; 24%). Eight studies were restricted to older patients ($N = 2514$; 10%) compared with all adult age groups in 53 ($N = 22\,279$; 90%). Twelve studies were conducted entirely within North America ($N = 10\,589$; 43%), whereas 49 were international in nature ($N = 14\,204$; 57%). Although data on prophylactic antibiotic use were collected, only nine trials specified antibiotic use, including five in which prophylactic antibiotics were mandated and four in which they were prohibited in all patients. Two studies specified prophylactic antibiotic use only with certain chemotherapy regiments. Most studies did not specify or present results related to prophylactic antibiotic use. There was no significant interaction between prophylactic antibiotic use and prophylactic G-CSF for mortality. Only three studies reported information related to erythropoietin use. Erythropoietin was mandated for all patients in one study [22], mandated in one arm only in one study [17], and there was a second randomization to erythropoietin in a third study [23]. The overall assessment of study quality was good. Fifty-one (84%) of studies presented justification for study sample size, whereas 55 (90%) provided an adequate description of statistical methods. Fifty-five (90%) studies described the flow of patients including 24 providing a detailed systematic description of patient flow. Adverse events were reported in all but one RCT (98%) and were systematically reported in 51.

meta-analysis

study heterogeneity. Significant heterogeneity was observed across all studies for RR of mortality ($Q = 89.7$, $P = 0.006$; $I^2 = 34\%$) but not for ARD. Importantly, no significant heterogeneity was observed among Group 1 or 2 studies , whereas significant heterogeneity was found among Group 3 and 4 studies. Of note, when analysis was limited to studies where treatment was for curative intent, no evidence of significant heterogeneity was observed.

mortality. The estimated RR and ARD for mortality across all RCTs were 0.93 (0.90–0.96; $P < 0.001$) and −3.2% (−2.1% to −4.2%) $P < 0.001$), respectively. A significant reduction in the RR for mortality was observed across trials with increasing duration of reported follow-up (Figure 2). Forty-three studies claimed to utilize ITT analysis of which 26 used a strict definition and 17 allowed limited exclusions. Of the remaining studies, seven clearly did not use ITT analysis and 11 were unclear. Significant differences in RR for mortality across studies were observed on the basis of the type of analysis ($P = 0.14$). Only those studies not utilizing ITT analysis failed to demonstrate a significant treatment effect.

The estimated RR and ARD for mortality by chemotherapy dose–schedule, cancer type and source of funding, treatment intention, primary outcome, age eligibility and study location are shown in Table 1. In combined analysis, the greatest reductions in all-cause mortality were seen in lymphoma (RR = 0.89; 0.84–0.95; $P < 0.0001$) and lung cancer patients (RR = 0.93; 0.88–0.98; $P = 0.005$). Likewise, significant

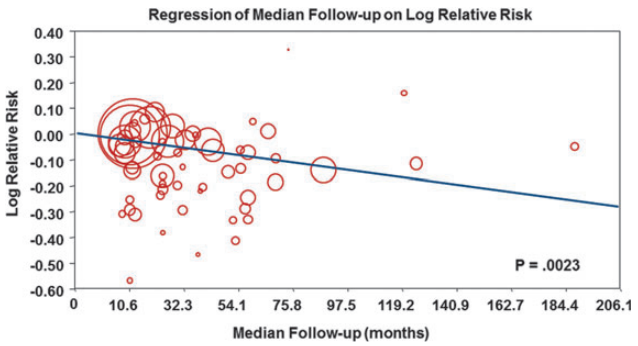

Figure 2. Meta-regression of the median follow-up on log RR of all-cause mortality: G-CSF-supported chemotherapy versus control. Each circle represents an individual study. The size of each circle is inversely proportional to the variance of the estimate. A significant reduction in the RR for mortality was observed across trials with increasing duration of reported follow-up.

Table 1. Relative risk and absolute risk decrease for all-cause mortality with G-CSF versus no G-CSF: by cancer type and regimen category

	Subgroup	*N*	RR	95% CLs	ARD (%)	95% CLs (%)
Regimen category	Group 1	15	0.959	0.915, 1.005	−2.8	−5.7, 0.1
	Group 2	12	0.893***	0.848, 0.940	−4.9***	−6.9, −2.8
	Group 3	18	0.917*	0.853, 0.985	−2.2*	−4.0, −0.4
	Group 4	16	0.941*	0.888, 0.996	−2.8**	−4.7, −0.9
Cancer type	Breast	20	0.954	0.898, 1.013	−1.5*	−2.9, −0.2
	Genitourinary	7	0.946	0.884, 1.013	−4.2*	−7.8, −0.7
	Lung	16	0.930**	0.882, 0.980	−5.6***	−8.5, −2.7
	Lymphoma	16	0.895***	0.841, 0.952	−4.8***	−7.1, −2.4
	Other	2	0.867	0.630, 1.193	−8.3	−18.0, 1.4
Source of funding	Government	14	0.947*	0.905, 0.992	−4.0**	−6.8, −1.2
	Industry	22	0.953*	0.911, 0.997	−2.3**	−3.8, −0.7
	Other	11	0.883***	0.825, 0.945	−3.6***	−5.5, −1.7
	Unknown	14	0.868**	0.788, 0.955	−4.3**	−7.2, −1.5
Treatment intention	Curative	26	0.913***	0.869, 0.959	−4.1**	−5.8, −2.4
	Non-curative	35	0.942**	0.910, 0.975	−2.6***	−4.0, −1.3
Stage	I–III	10	0.945	0.875, 1.021	−1.1	−2.6, 0.4
	IV	22	0.949	0.916,0.983	−3.5**	−5.8, −1.2**
	All stages	29	0.891	0.857, 0.927	−5.1***	−6.8, −3.3***
PS for eligibility	No	14	0.929*	0.872, 0.991	−1.7*	−3.2. −0.2
	Yes	47	0.921***	0.895, 0.946	−4.3***	−5.7, −2.9
PS description	No	17	0.901**	0.839, 0.968	−1.9**	−3.3, −0.6
	Yes	44	0.930***	0.906, 0.955	−4.4***	−6.0, −2.8
Prophylactic	Mandated	5	0.965	0.902, 1.032	−2.1	−6.6, 2.4
Antibiotics	Prohibited	4	0.945	0.826, 1.081	−3.3	−9.6, 2.9
	Mixed	2	0.983	0.749, 1.290	0.6	−1.5, 2.8
	Unknown	50	0.911***	0.877, 0.946	−4.2***	−5.5, −3.0
Primary outcome	Survival	37	0.912***	0.876, 0.950	−3.3***	−4.5, −2.1
	Other	24	0.976	0.941, 1.013	−2.7*	−4.8, −0.7
Age eligibility	Elderly only	8	0.898**	0.830, 0.971	−5.7**	−9.5, −1.8
	All ages	53	0.936***	0.906, 0.966	−2.9***	−3.9, −1.8
Study location	International	48	0.918***	0.891, 0.946	−4.4**	−5.7, −3.0
	USA only	13	0.980	0.942, 1.020	−1.2***	−2.7, −0.4

CLs, confidence limits; *N*, number of trials; PS, performance status. Group 1, same dose and schedule planned in study arms; Group 2, dose-dense versus standard treatment interval; Group 3, dose escalated versus standard dose and schedule; Group 4, single chemotherapy agent addition or substitution.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

reductions in mortality were observed in studies with treatment of both curative (RR = 0.91; 0.87–0.96; $P = 0.001$) and non-curative intent (RR = 0.94; 0.91–0.98; $P < 0.001$). Reductions in the risk of mortality were also observed for studies where survival was a primary outcome (RR = 0.91; 0.88–0.95; $P < 0.001$). Reductions in mortality were found for RCTs limited to elderly patients (RR = 0.90; $P = 0.007$) as well as those with all adult age groups permitted (RR = 0.94; $P < 0.001$). Likewise, reductions in the RR for mortality were observed regardless of funding source including government ($P = 0.011$), industry ($P = 0.043$) and other/unknown funding ($P < 0.001$). Both RR and ARD for all-cause mortality remain significant when the analysis is limited to larger studies with 300 or more patients.

Among the four categories of chemotherapy dose and schedule considered, significant reductions in the RR of mortality were observed in RCTs of dose-dense chemotherapy (RR = 0.89; 0.85–0.94; $P < 0.001$), dose escalation chemotherapy (RR = 0.92; 0.85–0.99; $P = 0.020$) and RCTs comparing intensified arms adding or substituting no more than one chemotherapy agent to control (RR = 0.94; 0.89–0.99; $P = 0.031$). A non-significant trend favoring reductions in the RR of mortality were observed for RCTs planning the same dose and the schedule of chemotherapy in each arm (RR = 0.96; 0.92–1.01; $P = 0.061$).

Figure 3 displays the results of the primary analysis presented as forest plots for the eligible studies in each of the dose and schedule design categories for each major cancer type. Among Group 1 studies, a significant reduction in mortality in those randomized to receive G-CSF support was observed in trials of patients with lymphoma with RR = 0.92 (0.85–0.99) and ARD = −4.2 (−8.5 to 0; $P = 0.050$). Similar but non-significant trends were found for other cancer types except breast cancer. Among Group 2 studies, a significant reduction in mortality was observed in RCTs in breast cancer [RR = 0.86 (0.75–0.98); ARD = −3.1% (−5.7 to −0.4); $P = 0.024$], GU cancer [RR = 0.87 (0.77–0.98); ARD = −11.4% (−20.8 to −2.1); $P = 0.016$) and lymphoma [RR = 0.83 (0.74–0.93); ARD = −6.2% (−10.0 to −2.5); $P = 0.001$] with a similar trend in the two trials in

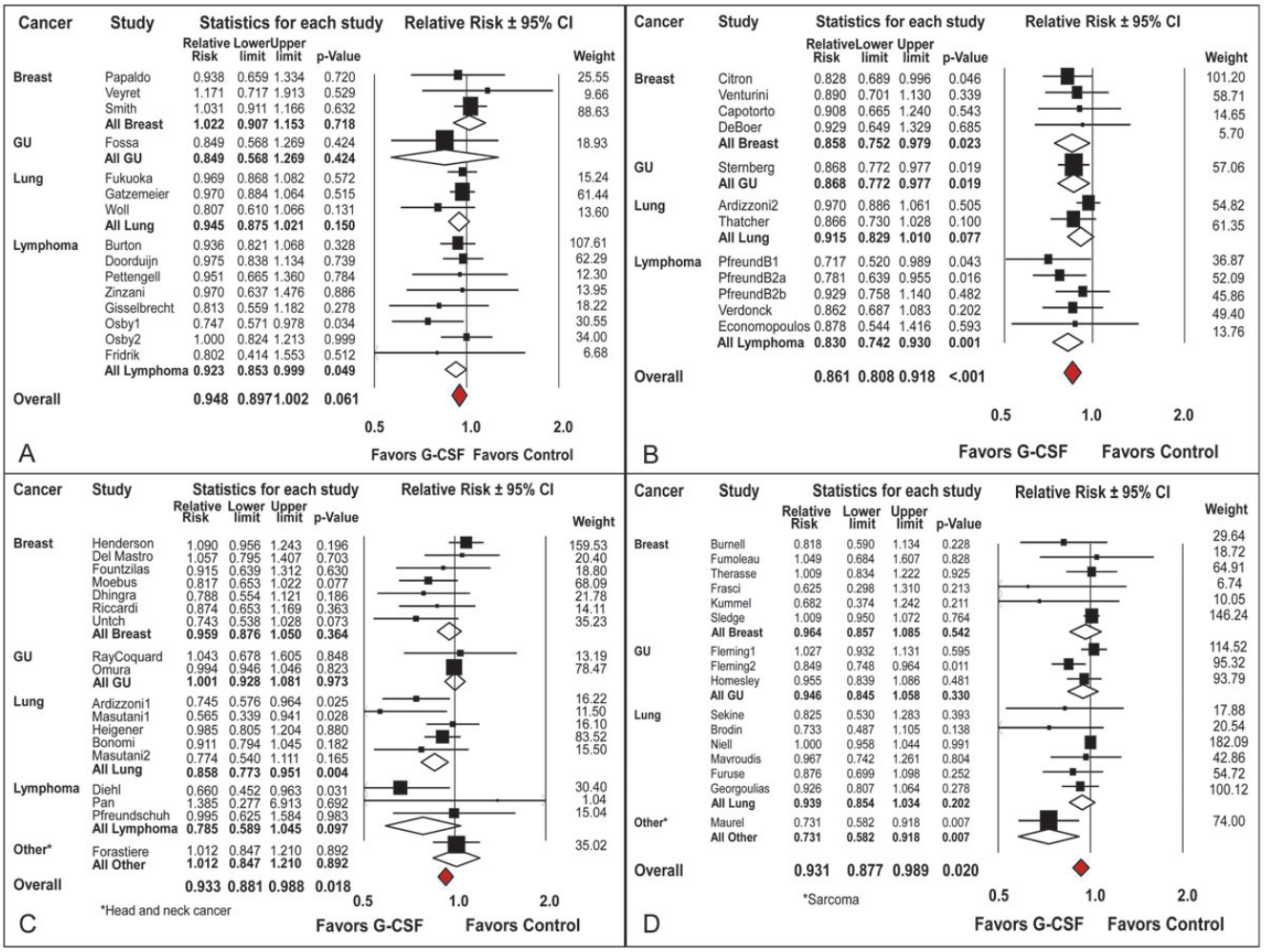

Figure 3. Results of primary analysis presented as forest plots for the eligible studies in each of the dose and schedule design categories for major cancer types. (A) RCTs planning the same dose and schedule of chemotherapy in each arm; (B) RCTs of dose-dense chemotherapy; (C) RCTs of dose escalation chemotherapy; (D) RCTs comparing intensified arms adding or substituting no more than one chemotherapy agent to control. Absolute weights based on study variance contribution to the overall summary estimates for each dose and schedule category are provided. The boxes displayed represent point estimates for RR for each study with 95% confidence intervals. The area of the box is proportional to the relative weight of each study within the cancer subgroup category.

lung cancer. Among Group 3 studies, a significant reduction in mortality was found among lung cancer trials [RR = 0.85 (0.74–0.98) 0.86 (0.77–0.95); ARD = −11.0% (−19.3 to −2.7); $P = 0.023$] with non-significant trends among other disease subgroups. Among Group 4 studies, a significant RR reduction in mortality was seen in the only sarcoma trial and one of the GU trials but otherwise, significant treatment effects were not found within the subgroups analyzed. Similarly, Figure 4 displays the results of the primary analysis presented as forest plots for the eligible studies in each of the dose and schedule design categories for survival as the primary or a secondary study outcome. The strongest treatment effects in this exploratory analysis when survival was the primary study outcome were observed for dose-dense studies and for drug addition or substitution studies.

relative dose intensity. The median planned RDI was 1.00, 1.50 and 1.58 in Group 1, 2 and 3 studies, respectively. Among the 31 randomized comparisons with the same agents in both arms reporting delivered RDI, the mean (median) delivered chemotherapy RDI was 1.21 (1.14) with G-CSF support compared with 0.92 (0.95) among controls. The median delivered RDI was 1.05, 1.48 and 1.56 in Group 1, 2 and 3 studies, respectively. Likewise, Figure 5 displays the mean ± 95% CI for both planned and delivered RDIs by dose–schedule groups. In exploratory analysis, the association between RDI and greater reduction in mortality was significant in studies where survival was the primary outcome ($P = 0.0043$). Figure 6 displays meta-regressions of RDI (Figure 6A) and absolute difference in dose intensity (Figure 6B) on the RR for mortality.

study quality and publication bias. All studies included in this meta-analysis were RCTs of which the majority were judged to be moderate to high quality based on the parameters assessed including whether survival was the primary outcome of the study. No significant differences in treatment effect were observed across the limited range of summary quality scores.

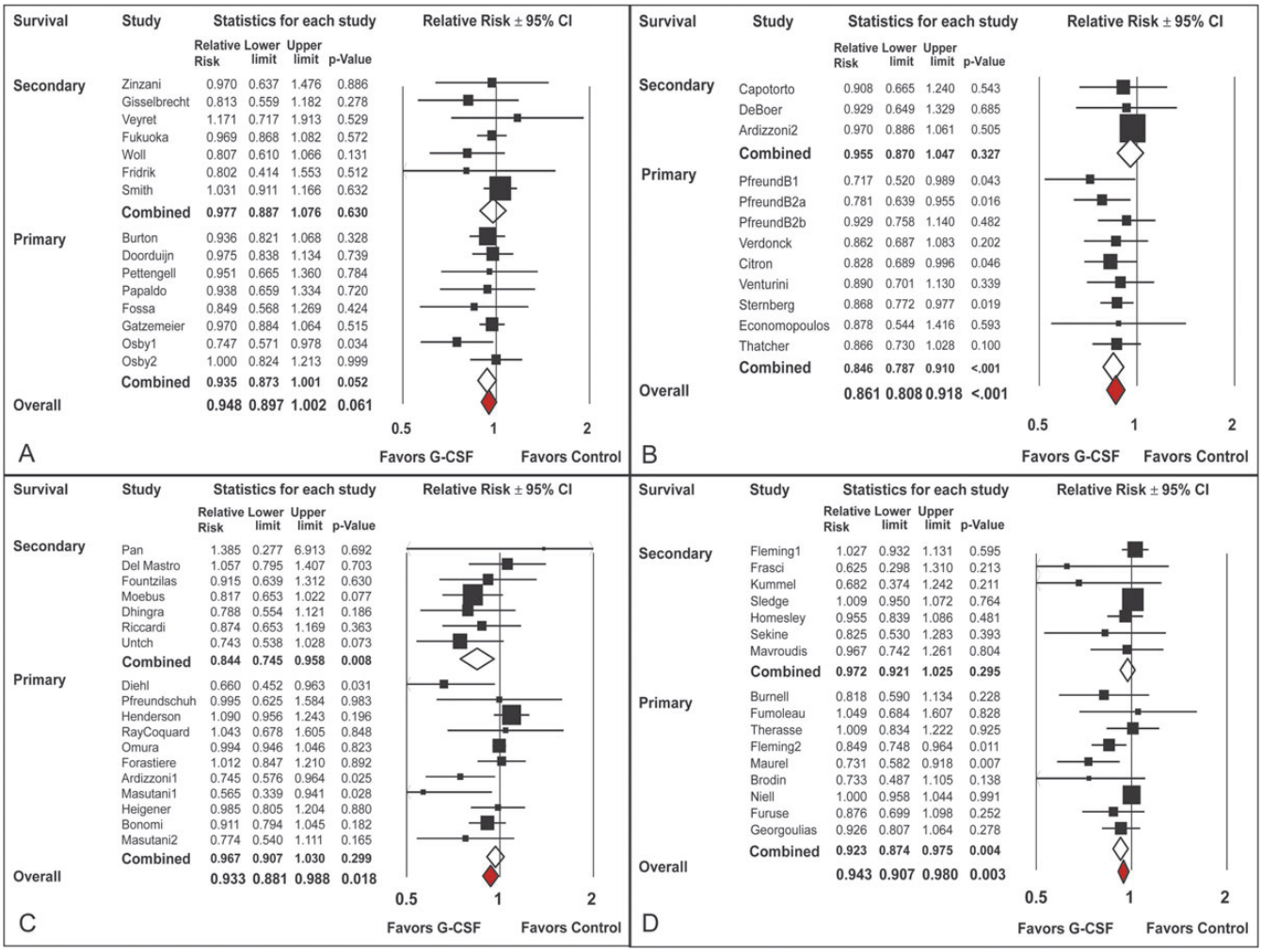

Figure 4. Results of primary analysis presented as forest plots for the eligible studies in each dose and schedule design category stratified by survival as a primary or a secondary study outcome. (A) RCTs planning the same dose and schedule of chemotherapy in each arm; (B) RCTs of dose-dense chemotherapy; (C) RCTs of dose escalation chemotherapy; (D) RCTs comparing intensified arms adding or substituting no more than one chemotherapy agent to control. Absolute weights based on study variance contribution to the overall summary estimates for each dose and schedule category are provided. The boxes displayed represent point estimates for RR for each study with 95% confidence intervals. The area of the box is proportional to the relative weight of each study within the cancer subgroup category.

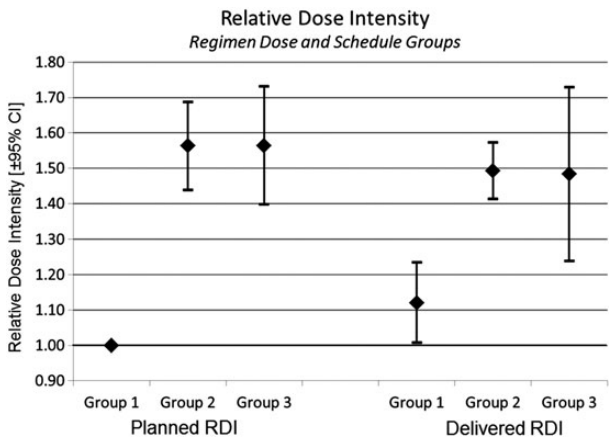

Figure 5. Displays of the mean ± 95% CI for both planned and delivered RDI with G-CSF-supported chemotherapy versus control by the chemotherapy dose and schedule group.

Figure 7 displays funnel plots of precision and the log RR of call-cause mortality for studies based on dose and schedule planned along with imputed missing studies and adjusted RR estimates. Evidence of a funnel plot asymmetry was found across all eligible studies based on Egger's regression intercept ($P < 0.0001$) and Kendall's tau statistic ($P = 0.0446$). No evidence for significant publication bias for studies of the same planned dose and schedule (Group 1) or dose-dense schedules (Group 2), whereas evidence of significant publication bias was observed among chemotherapy dose escalation studies (Group 3) and drug addition or substitution studies (Group 4).

discussion

This study presents results on 59 individual RCTs (61 separate comparisons) involving nearly 25 000 patients with solid tumors or lymphoma randomized to receive cancer chemotherapy with or without primary G-CSF support and

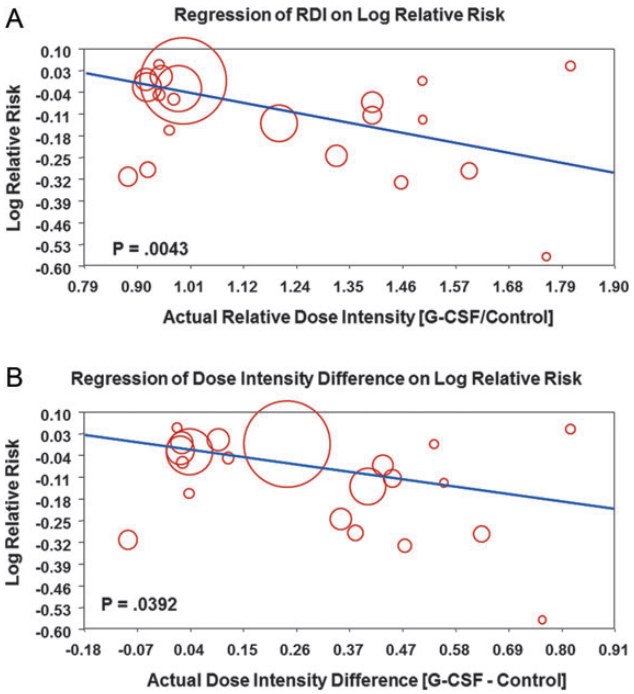

Figure 6. Meta-regression of RDI on log RR of all-cause mortality with G-CSF-supported chemotherapy versus control. Each circle represents an individual study. The size of each circle is inversely proportional to the variance of the estimate. Significant reductions in the RR for mortality were observed across trials where survival was the primary outcome with increasing actual RDI (A) and actual dose intensity difference (B).

reporting at least 2 years of follow-up for overall mortality. The risk of all-cause mortality over the period of observation in these studies was 38% and was significantly lower in patients receiving G-CSF-supported chemotherapy than among controls (RR = 0.93; ARD = −3.2%). The reduced risk for mortality with G-CSFs was seen across cancer types and dose and schedule categories. Of interest, greater reductions in risk for all-cause mortality were observed in studies with longer follow-up. The primary analysis of all-cause mortality within the four preplanned dose–schedule design study groups demonstrated significant reductions in the relative and absolute risks of mortality for dose-dense (Group 2) schedules and dose escalation (Group 3) schedules with G-CSFs compared with controls. The greatest reductions in the relative and the absolute risk of mortality were observed in patients receiving greater RDI, most notably in those randomized to dose-dense regimens. In same dose–schedule trials (Group 1), a non-significant trend toward a reduction in all-cause mortality was observed ($P = 0.061$) along with a significant increase in mean delivered RDI in study arms supported by G-CSFs compared with controls likely due to few dose reductions and delays among control subjects.

In preplanned subgroup analyses, the greatest reductions in the risk of mortality in G-CSF-supported patients were observed when patients were treated for curative intent and in studies where survival was the primary outcome. In the later setting, a significant trend between increasing RDI and improved survival was observed. In subgroup analyses, reductions in the risk of mortality across tumor types were observed with the greatest

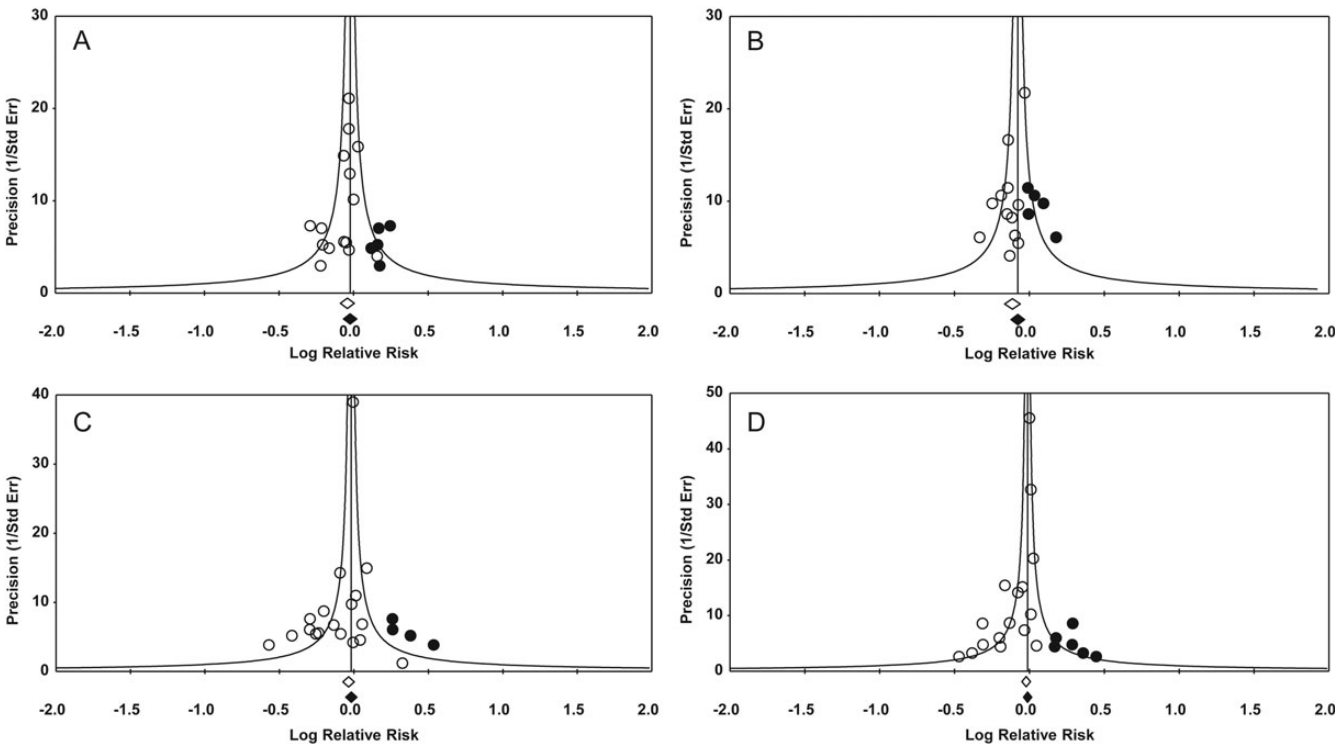

Figure 7. Funnel plots of precision by log RR of all-cause mortality by chemotherapy dose and schedule planned. In analyses based on the four study chemotherapy dose and schedule regimens, no evidence for significant publication bias for studies of the same planned dose and schedule (A) or dose-dense schedules (B). Evidence of significant publication bias for treatment effect was found among chemotherapy dose escalation studies (C) and drug addition or substitution studies (D). Estimated missing studies (solid circles) and adjusted pointed estimates (solid diamonds) were based on the trim and fill method of Duval and Tweedie.

treatment effects seen in patients with lymphoma and lung cancer. Significant reductions in mortality with G-CSF-supported chemotherapy appeared to be independent of the study age group as well as the source of funding. Evidence for publication bias based on the funnel plot asymmetry was observed when all studies were combined and in dose–schedule groups 3 and 4 but not among Group 1 and 2 dose-scheduled groups or where patients were treated with curative intent. When survival was reported as the primary outcome, a significant inverse association was observed between RDI and the RR for all-cause mortality.

There are potential limitations to the study reported here that should be noted. Systematic reviews may fail to identify all potentially important studies in the world's literature as not all journals are indexed in the commonly utilized electronic databases. However, the search undertaken here was exceptionally broad and inclusive. It is unlikely that large high-quality RCTs would have failed to make their way into the mainstream medical literature incorporated into the searchable databases studied here. As in the majority of meta-analyses in oncology, this study represents an aggregate meta-analysis and is not based on individual patient data and thus may be prone to ecological fallacy. In addition, it is likely that many patients in the control arms of these studies subsequently received G-CSFs as permitted by the study or off protocol. Therefore, later exposure to G-CSFs among the control patients in these studies cannot be excluded. There are insufficient data on the dose and the duration of G-CSFs in the majority of studies included in this analysis. The survival data abstracted were that presented by the authors of the original studies at the time of their analysis. Since the intention of the study was to evaluate the long-term outcome, there was a requirement of the minimum follow-up for study to be eligible for our systematic review. Two years was chosen as representing treatment outcomes well beyond the initial treatment and having some degree of relevance for all cancer types encountered.

Although no significant differences in treatment effect on mortality were found based on the use or restriction of prophylactic antibiotics, the majority of studies did not report antibiotic use in these trials. Although the use of ITT analysis did vary across the trials included in this analysis, only studies clearly not using ITT failed to demonstrate a significant treatment effect.

An inherent limitation of RCTs included in this or any study level meta-analysis is the often selected nature of eligible patients often excluding those with certain comorbidities or poor performance. This may be particularly relevant to evaluating the efficacy and safety of intensified chemotherapy programs especially when evaluating less commonly studied disease settings and patient subgroups. It is reassuring, nonetheless, that similar effects on the net impact on patient outcomes represented by all-cause mortality were observed for less commonly studied settings such as genitourinary and lung malignancies and the most favorable estimate of treatment effect was observed in the 'other' disease category. Likewise, very similar favorable effects on all-cause mortality were observed in studies using performance status for eligibility or not as well as regardless of treatment intent, disease stage and in studies limited to elderly patients. Finally, the potential for publication bias must also be kept in mind as not all clinical trials, including RCTs, may be published for a variety of reasons. The significant funnel plot asymmetry was observed across all studies but not among studies limited to patients treated for curative intent.

In conclusion, primary G-CSF support of systemic cancer chemotherapy is associated with significantly greater planned and delivered chemotherapy dose intensity compared with controls without G-CSF support. Importantly, the primary G-CSF support of chemotherapy is associated with significantly greater relative and absolute risk reductions in all-cause mortality.

disclosure

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Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer

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Neoadjuvant therapy is increasingly becoming a valid treatment option for patients with locally advanced pancreatic cancer (LAPC). In borderline resectable disease, neoadjuvant therapy is employed to improve the probability of margin-clear resections. In non-metastatic, non-resectable pancreatic cancer, treatment primarily aims to induce disease control, but may achieve conversion to surgical resectability in some patients. Several treatment modalities including chemotherapy, chemoradiotherapy (CRT) or the sequential use of both have been investigated in numerous, mostly small and non-randomized studies. Nevertheless, there is a consistent finding that neoadjuvant therapy can induce resectability in up to 30%–40% of LAPC patients. Once resection has been achieved, overall survival appears to be comparable to that observed for primarily resectable patients. Thus, patient selection evolves as an important aspect of neoadjuvant therapy; retrospective analyses identified induction chemotherapy as an appropriate tool to define LAPC patients who may benefit most from subsequent treatment with CRT. The clinical importance of induction chemotherapy may further increase once highly active protocols such as the FOLFIRINOX or the gemcitabine plus nab-paclitaxel regimen are introduced into novel multimodality treatment concepts.

Key words: chemoradiotherapy, chemotherapy, neoadjuvant, pancreatic cancer

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