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Relative Dose Intensity of Chemotherapy and Survival in Patients with Advanced Stage Solid Tumor Cancer: A Systematic Review and Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Carboplatin-based regimens • FOLFOX/FOLFIRI-based regimens • Meta-analysis • Overall survival • Progression-free survival • Relative dose intensity

Abstract

Background. Chemotherapy-induced toxicities lead to therapy dose reduction or delay, affecting patient outcomes. This systematic review and meta-analysis evaluated the impact of relative dose intensity (RDI) on survival in adult patients with solid tumor cancer on nonadjuvant-based chemotherapy regimens.

Methods. PubMed, Embase, and Web of Science databases were searched for peer-reviewed English journal articles or congress abstracts evaluating association between RDI and survival; observational studies, case series of ≥20 patients, and clinical trials published between 2013 and 2020 were eligible. Meta-analyses were conducted to quantify the association between RDI levels and overall survival (OS) among studies reporting a hazard ratio (HR) for OS by similar tumor types, regimens, and RDI. Forest plots represented summary HR and 95% confidence interval (CI); Cochran's Q and I^2 tests evaluated study heterogeneity.

Results. Overall, 919 articles were reviewed and 22 included; seven were eligible for meta-analysis. Significantly shorter OS at RDI <80% versus ≥80% and <85% versus ≥85% was observed upon meta-analysis of four carboplatin-based studies for breast, non-small cell lung, or ovarian cancer (HR 1.17; 95% CI: 1.07–1.27) and three FOLFOX-, FOLFIRI-, or FOLFIRINOX-based studies for colorectal or pancreatic cancer (HR 1.39; 95% CI: 1.03–1.89). Grade 3 or higher hematologic toxicities were higher for carboplatin-based regimens (thrombocytopenia: 14%–22%; anemia: 15%–19%; neutropenia: 24%–58%) than FOLFOX-, FOLFIRI-, or FOLFIRINOX-based regimens (thrombocytopenia: 1%–4%; anemia: 5%–19%; neutropenia: 19%–47%).

Conclusion. The results suggested longer OS with RDI ≥80% or ≥85% for both regimens, indicating that management of toxicities across treatment modalities may contribute to maintenance of higher RDI and benefit survival for patients with advanced solid tumors. ***The Oncologist*** 2021;26:e1609–e1618

Implications for Practice: Chemotherapy-induced toxicities lead to dose reduction and/or treatment delay, thus affecting patient outcomes. Results of this systematic review and meta-analysis, evaluating the impact of relative dose intensity (RDI) on survival of patients with solid tumors on nonadjuvant-based chemotherapy regimens, demonstrate a longer overall survival with RDI levels of at least 80% for patients with solid tumors on carboplatin-based and FOLFOX-, FOLFIRI-, or FOLFIRINOX-based chemotherapy regimens, suggesting a protective effect of maintaining RDI ≥80% or ≥ -85%. Although grade 3 or higher hematologic toxicities occurred more in carboplatin-based studies, managing toxicities across treatment regimens may contribute to maintenance of higher RDI and ultimately benefit overall survival.

Introduction

Chemotherapy-induced toxicities are a persistent challenge to optimal treatments and dosing regimens for patients with cancer [1, 2]. Although most chemotherapy regimens are dosed based on patient-specific parameters (body surface

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area or body weight), these regimens are often complicated by the occurrence of severe to life-threatening conditions, including febrile neutropenia, anemia, and thrombocytopenia, thus warranting a reduction in dose or delay in planned treatment [2, 3]. However, clinical evidence suggests that improved outcomes are achieved with standard chemotherapy regimens in a dose-dependent manner; patients receiving higher dose intensities experience better overall survival (OS), progression-free survival (PFS), and disease-free survival than patients receiving lower dose intensities than planned [1, 4, 5].

Relative dose intensity (RDI), the ratio of the delivered dose intensity (dose per unit body surface area per unit time [mg/m^2 per week]) to the standard or planned dose intensity for a chemotherapy regimen, is a summary measure commonly used to describe dose delays and/or reductions occurring with a chemotherapy regimen [1, 4]. A decrease in RDI below 85% (or below 80% in some studies) has been considered to be a clinically significant reduction from standard or planned therapy, and maintaining RDI has been associated with improved survival in advanced ovarian and breast cancer in both randomized clinical trials and retrospective observational studies [4–8].

Clinical practice surveys have shown that a substantial proportion of patients are treated at relatively low dose intensities, representing a potential reason for treatment failure in patients with curable malignancies [9]. A systematic review of the impact of RDI on survival in patients with metastatic lung, breast, or ovarian cancer receiving chemotherapy between January 2000 and April 2013 [1] concluded that maintaining an RDI of ≥85% had a favorable impact on survival. No reviews have since been published regarding the effects of RDI on a broader population of patients with cancer receiving chemotherapy. Thus, the purpose of this systematic review and meta-analysis was to evaluate the impact of RDI, including dose delays and reductions, on survival in patients with solid tumor cancer receiving nonadjuvant-based chemotherapy in publications from 2013 through 2020.

Materials and Methods

Study Search

The review was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. A systematic literature search was performed in PubMed, Embase, and Web of Science databases to identify peer-reviewed English journal articles or congress abstracts, and ClinicalTrials.gov to identify clinical trials with results reporting the impact of RDI or therapy dose delays and/or dose reductions on survival in adult patients with cancer treated with nonadjuvant-based chemotherapy. No other gray literature was considered. Search strings included terms for neoplasms, RDI, and survival (supplemental online Table 1). The search strategy was adapted to meet the search specifications of each included database and was designed to capture outcomes of interest and stratification variables in the scope of the literature review. These were translated into indexed Medical Subject Headings (MeSH) and plain language text-word terms using the National Library of Medicine MeSH thesaurus. Boolean operators were used to combine the final list of search terms into a comprehensive search strategy adding limit filters of language and date to ensure only the most relevant studies were included in the final search yield. Studies published prior to 2013 were filtered in the initial review of search results based on the Havrilesky et al. 2015 review article having an upper date limit of 2013 [1].

Study Selection

Study selections were documented through DistillerSR, a specialized software program designed for tracking and managing literature reviews, resulting in a fully auditable and transparent review process. Study eligibility criteria were defined a priori by study population, interventions, and outcomes (Table 1). Studies reporting a measure of RDI or treatment dose delays and/or reductions and evaluating overall and/or progression-free survival were included. Eligible publications included prospective or retrospective observational studies, case series of ≥20 patients, and clinical trials. Studies reporting RDI and the cumulative incidence of grade 3 or higher hematologic toxicities during treatment were also evaluated. Articles identified in the literature searches were uploaded into DistillerSR and de-duplicated by title and author. Studies were then screened by title and abstract against the inclusion and exclusion criteria; 10% of the abstracts were evaluated by an independent reviewer for quality control (QC). Articles designated as relevant were evaluated at full-text level by two reviewers independently to determine agreement on inclusion (100% QC). The screening results were recorded, maintained, and assessed using DistillerSR.

Data Extraction and Synthesis

Data were extracted in DistillerSR for all studies deemed relevant to the current analysis in the full-text review stage. The abstraction form was reviewed before any data extraction to ensure that all appropriate fields were captured, and an initial small sample of articles was extracted to determine that the form was able to capture the appropriate information from the articles. Specific items extracted included study characteristics (study design, duration, follow-up time, inclusion and exclusion criteria, and patient demographics), disease characteristics (tumor type, tumor stage, and previous therapies or surgeries), treatment characteristics (treatment regimen, dosage, number of cycles, concomitant treatment, RDI, and dose delays and/or reductions), and prevalence of dose-limiting toxicities (neutropenia, thrombocytopenia, leukopenia, fatigue, etc.).

Risk of Bias and Study Quality Assessment

Studies were evaluated for risk of bias and study quality using several methods based on study design. Case-control and cohort studies were assessed using the Newcastle-Ottawa Scale [11], and clinical trials were assessed using the Cochrane Risk of Bias Tool [12]. The Newcastle-Ottawa Scale score ranges from 0 to 9, with lower scores indicating higher risk of bias and higher scores indicating lower risk of bias. The Cochrane Risk of Bias Tool scores studies as having a low risk of bias, some concerns for risk of bias, or high risk of bias using five bias domains. The approach to address

Table 1. Inclusion and exclusion criteria for narrative review and meta-analysis

Inclusion criteria	Exclusion criteria
Adult patients with cancer with solid tumors, regardless of tumor location or stage. ► **Limited to breast, ovarian, and pancreatic cancer and NSCLC and CRC.**[a]	Studies of patients without cancer, pediatric patients, or patients with blood tumors (leukemia, lymphoma, myeloma).
Studies evaluating nonadjuvant chemotherapy regimens providing a measure of RDI. ► **Limited to carboplatin-based or FOLFOX- or FOLFIRI-based regimens.**[a]	Studies without evaluation of chemotherapy regimens or only including adjuvant therapies, alternative, homeopathic, naturopathic, or traditional Chinese regimens.
Studies including comparison of different levels of RDI ► **Limited to RDI comparisons of <85% vs. ≥85% or <80% vs. ≥80% (including one study of <79% vs. ≥79%).**[a]	Studies without any RDI level comparisons.
Studies evaluating survival measures, such as overall, disease-free, or progression-free survival. ► **Limited to overall survival.**[a]	Studies not evaluating any survival measures.
Studies published in English from 2013 to 2019. Prospective or retrospective observational cohort studies, clinical trials, case-control studies, and case series with $n \geq 20$ were eligible.	Studies not published in English, studies published prior to 2013, nonhuman studies (laboratory, preclinical, or animal studies), case series with <20 patients, opinion pieces, reviews, and case reports.

[a]Bold text indicates an additional criterion imposed for inclusion of articles for the meta-analysis after a review of characteristics of studies identified through initial literature review. Non-bold text indicates original study eligibility criteria from the systematic literature review.
Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; FOLFOX, folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin; NSCLC, non-small cell lung cancer; RDI, relative dose intensity.

the potential for differences in baseline prognostic factors such as tumor stage and Eastern Cooperative Oncology Group performance status between RDI levels was evaluated for each study. During the systematic literature review, we abstracted patient factors, including sex, race, time from diagnosis, dosing regimen, comorbidities, earlier therapies, and treatment line number. Our primary concern for observational studies was confounding of the RDI-survival association by disease stage. The risk of bias tool for cohort studies addressed whether tumor stage was used as an adjustment factor in the analyses, and studies restricting inclusion to a particular subpopulation (e.g., all patients with stage II–III colon cancer) were noted.

Statistical Analysis

Fixed-effect meta-analyses were conducted based on the results of the systematic review. Studies eligible for meta-analysis reported a hazard ratio (HR) for OS and were categorized by tumor type, chemotherapy regimen, and evaluated RDI threshold(s). Categories that contained at least three studies were included for meta-analysis. Studies that used an RDI threshold of 80% and those that used a threshold of 85% were not separated into distinct meta-analyses because these thresholds were considered sufficiently similar. Specific thresholds used in each study are reported throughout results tables and figures. The primary objectives of the meta-analysis were to determine the summary strength of association between lower and higher RDI levels (<80% vs. ≥80% or < 85% vs. ≥85%) of carboplatin-based chemotherapy regimens and OS in studies of ovarian or breast cancer or non-small cell lung cancer (NSCLC), and the summary strength of association between lower and higher RDI levels (<80% vs. ≥80% or < 85% vs. ≥85%) of FOLFOX- or FOLFIRI-based chemotherapy regimens and OS in studies of colorectal cancer (CRC) or pancreatic cancer. Fixed-effect meta-analyses of HRs were conducted using Comprehensive Meta-Analysis software (version 3.0; Biostat, Englewood, NJ). The effect of chemotherapy RDI on survival was summarized, weighting all included studies by the inverse of their variance [13]. Forest plots were used to represent HRs and 95% confidence intervals (CIs); values of $p < .05$ were considered significant.

Potential sources of heterogeneity in the impact of RDI on survival in each analysis were evaluated using the Cochran's Q and I^2 statistical tests. The I^2 statistics indicate the percentage of systematic variability across studies (range: 0%–100%), with larger values depicting greater heterogeneity [14].

Results

Search Results

Figure 1 shows a PRISMA flow diagram detailing the flow of study inclusion and exclusion at each level, with reasons for exclusion at the full-text level. We identified 1,442 English language articles from the three databases (Fig. 1). After removing duplicate articles, 919 studies were screened at the level of title and abstract; 789 studies were assessed at the full-text level. Overall, 623 studies were excluded, primarily because they were published prior to 2013 ($n = 351$) or they only evaluated adjuvant or neoadjuvant therapies ($n = 113$). In total, 166 studies were eligible for inclusion, among which 137 did not report any comparison between the RDI levels and seven belonged to the same trial or cohort. Finally, 22 studies were included in the abstraction database; seven were eligible for meta-analysis. Most of the studies used the Hryniuk calculation method [15] to assess the ratio of the actual or delivered dose intensity to the planned or standard dose intensity. The method used to calculate RDI was not cited by all of the included studies.

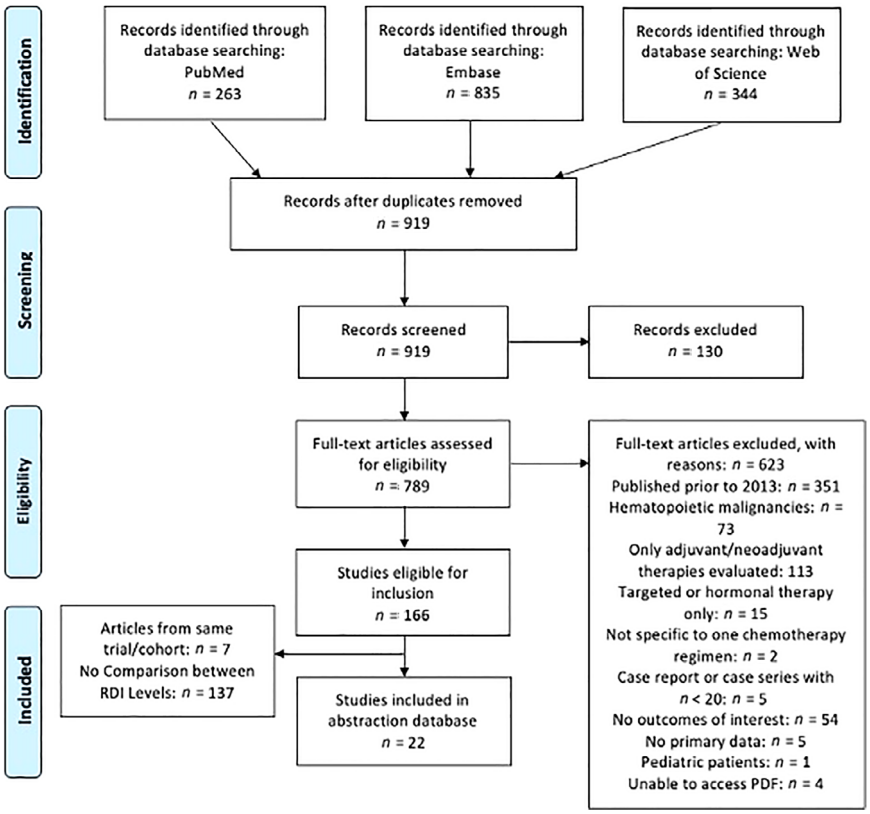

Figure 1. PRISMA diagram for study inclusion. Source: Moher et al. [10].
Abbreviation: RDI, relative dose intensity.

Clinical Characteristics of Selected Studies

Of the 22 included studies, 6 (27.3%) evaluated pancreatic cancer, 4 (18.2%) ovarian cancer, 3 (13.6%) CRC, 3 (13.6%) gastric cancer, 2 (9.1%) breast cancer, 1 (4.5%) esophageal cancer, 1 (4.5%) prostate cancer, 1 (4.5%) NSCLC, and 1 (4.5%) lung cancer. Interventions included platinum-based regimens (9 [40.9%]), FOLFIRI-, FOLFOX-, or FOLFIRINOX-based regimens (5 [22.7%]), taxane-based regimens (8 [36.4%]), and irinotecan monotherapy (1 [4.5%]). Most of the studies were observational (21 [95.5%]), with only one clinical trial (4.5%); 11 (50%) of the studies were conducted in Japan, followed by the U.S. (3 [13.6%]), Spain (2 [9.1%]), Australia (2 [9.1%]), China (1 [4.5%]), South Korea (1 [4.5%]), Denmark (1 [4.5%]), and 1 (4.5%) in multiple countries.

Outcomes of the Systematic Literature Review

The studies included in the systematic literature review ($n = 22$) [5, 16–36] were grouped by chemotherapy regimen. Most studies reported outcomes of OS or PFS. Eight studies reported median OS [16–21] and PFS [16–19, 22, 23] but not HR. RDI cutoffs ranged from 0% (vs. 100%) for 5-fluorouracil bolus [22] to 80%, 85%, or 90% in several studies describing FOLFIRI-, FOLFOX-, or FOLFIRINOX-based regimens [28–31], including one with RDI cutoff of 77% [17] and one with RDI 79% [29]. The differences in OS between RDI categories were up to approximately 14 months [16, 17, 18, 19, 29, 32, 33]. For convenience in the following results summary, we considered a difference of at least 1 month to be clinically significant; however, the choice of this value is subjective and may vary by patient population and tumor type. Where survival time differences were statistically compared, we reported the level of significance in Figures 2 and 3. Of the 10 studies that reported median OS in high and low RDI categories, six reported at least 1 month longer OS with higher than with lower RDI [16, 22, 23, 29, 30, 32], three did not show any significant difference within 1 month [18, 19, 33], and one reported at least 1 month longer median OS with lower than with higher RDI [18] (Fig. 2). Three of the comparisons that reported more than 1 month longer median OS with higher RDI reported $p < .05$ for the difference, and all were for <80% versus ≥80% RDI (Fig. 2). Nine studies reported median PFS in high and low RDI categories, among which five reported at least 1 month longer PFS with higher than with lower RDI [16, 24, 26, 29, 32], three reported no significant differences within 1 month [18, 19, 24], and two reported at least 1 month longer median PFS with lower than with higher RDI [17, 22] (Fig. 3). Six comparisons reporting more than 1 month longer median PFS with higher RDI reported significance level of $p < .05$; one study of FOLFIRI in patients with CRC reported longer median PFS with RDI below 60% ($p < .05$; Fig. 3). Seven studies reported both OS and PFS [16–19, 22, 29, 32]. In one study of patients with metastatic CRC on oxaliplatin and irinotecan-based chemotherapy regimens, PFS increased slightly with higher RDI, whereas OS remained unchanged in the mFOLFOX6 regimen (modified FOLFOX, six cycles postoperative); both OS and PFS increased with higher RDI with the FOLFIRI regimen [29]. Conversely, in another study on patients with metastatic CRC, OS increased, whereas PFS decreased with higher RDI of ramucirumab plus modified FOLFIRI [22]. Higher RDI of nab-paclitaxel improved OS and PFS in a study on

Author	Year	Tumor type	Treatment	RDI threshold
Nakayama	2014	CRC	mFOLFOX6 (oxaliplatin)	79%
Nakayama*	2014	CRC	FOLFIRI (irinotecan)	80%
Au-Yeung	2014	ovarian	Paclitaxel	85%
Au-Yeung	2014	ovarian	Paclitaxel and carboplatin	85%
Au-Yeung	2014	ovarian	Carboplatin	85%
Yamashita**	2016	esophagus	Nedaplatin/5-fluorouracil	70%
Yamashita**	2016	esophagus	Nedaplatin/5-fluorouracil	60%
Yamashita**	2016	esophagus	Nedaplatin/5-fluorouracil	50%
Lee*	2017	pancreas	FOLFIRINOX	80%
Lee	2017	pancreas	FOLFIRINOX	70%
Lee**	2017	pancreas	FOLFIRINOX	55%
Kanazawa*	2017	gastric	Nab-paclitaxel	80%
Ishigaki	2017	pancreas	Nab-paclitaxel and gemcitabine	77%
Makiyama	2018	gastric	Irinotecan	80%
Fernandez	2018	pancreas	Nab-paclitaxel and gemcitabine	85%
Yoshihiro	2019	CRC	FOLFIRI	60%
Crawford	2020	NSCLC	Carboplatin or cisplatin combinations	85%

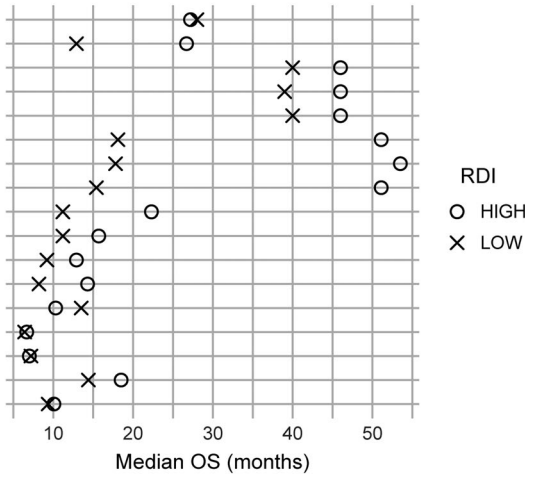

Figure 2. Median OS by RDI category. * Indicates $p < .05$ reported for the difference in median OS; ** indicates $.05 \leq p < .10$. Unmarked comparisons reported $p > .10$ or did not report p values.
Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; FOLIRINOX, folinic acid (leucovorin), fluorouracil (5-FU), irinotecan, and oxaliplatin; mFOLFOX6, modified folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin (six cycles postoperative); NSCLC, non-small cell lung cancer; OS, overall survival; RDI, relative dose intensity.

Author	Year	Tumor type	Treatment	RDI threshold
Shen*	2013	esophagus	Etoposide-platinum or paclitaxel carboplatin	80%
Nakayama**	2013	CRC	mFOLFOX6 (oxaliplatin)	79%
Nakayama	2013	CRC	mFOLFOX6 (oxaliplatin) and bevacizumab	76%
Nakayama*	2013	CRC	FOLFIRI (irinotecan)	80%
Nakayama	2013	CRC	FOLFIRI (irinotecan) and bevacizumab	76%
Nakayama*	2014	CRC	mFOLFOX6 (oxaliplatin)	79%
Nakayama*	2014	CRC	FOLFIRI (irinotecan)	80%
Au-Yeung	2014	ovarian	Paclitaxel	85%
Au-Yeung	2014	ovarian	Paclitaxel and carboplatin	85%
Au-Yeung*	2014	ovarian	Carboplatin	85%
Kanazawa*	2017	gastric	Nab-paclitaxel	80%
Ishigaki	2017	pancreas	Nab-paclitaxel and gemcitabine	77%
Makiyama	2018	gastric	Irinotecan	80%
Fernandez	2018	pancreas	Nab-paclitaxel and gemcitabine	85%
Yoshihiro*	2019	CRC	FOLFIRI	60%

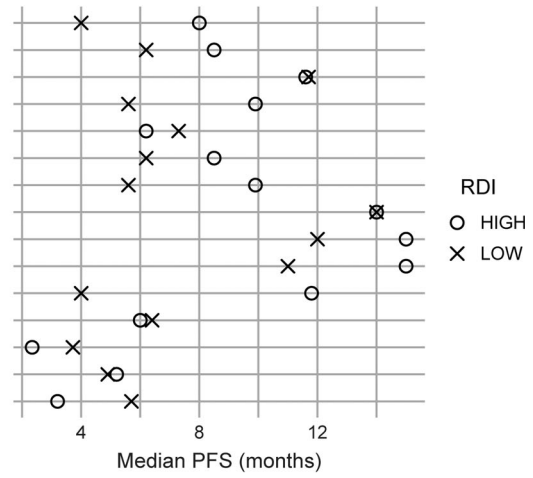

Figure 3. Median PFS by RDI category. * Indicates $p < .05$ reported for the difference in median PFS; ** indicates $.05 \leq p < .10$. Unmarked comparisons reported $p > .10$ or did not report p values.
Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; mFOLFOX6, modified folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin (six cycles postoperative); PFS, progression-free survival; RDI, relative dose intensity.

patients with advanced/recurrent gastric cancer [16], whereas another study reported improved OS with lower RDI of gemcitabine plus nab-paclitaxel in unresectable pancreatic cancer [17]. No difference in OS and PFS was observed with change in RDI in two studies in advanced gastric cancer [18] and metastatic pancreatic cancer [19].

Taxane (paclitaxel, nab-paclitaxel, docetaxel) and gemcitabine-based regimens were reported in eight studies of patients with breast, pancreatic, prostate, or gastric cancer (supplemental online Table 2). RDI cutoffs ranged from 63.6% [30] to 90% [27]. Kushnir et al. reported significantly improved OS of patients with metastatic castrate-sensitive prostate cancer per 10% increase in RDI of docetaxel [31]. Low RDI levels were associated with decreased OS and PFS in three studies [16, 32], whereas no significant associations between RDI and OS and/or PFS were identified in four studies [17, 19, 27, 30].

Meta-Analysis Results

Overall, seven studies were included in two separate meta-analyses (Table 2). The narrative summary identified two major categories for meta-analyses, all evaluating RDI levels <80% versus ≥80% or < 85% versus ≥85%: (a) carboplatin-based regimens for breast or ovarian cancer or NSCLC and (b) FOLFOX-, FOLFIRI-, or FOLFIRINOX-based regimens for

Table 2. Studies included in the meta-analyses, 2013–2019 (overall survival)

Author, year	Tumor type	Chemotherapy	Dosage	*n*	RDI comparison
Studies evaluating carboplatin-based regimens for ovarian or breast cancer or NSCLC					
Bun 2019 [33]	Ovarian	Paclitaxel/carboplatin	PPaclitaxel (80 mg/m2 on days 1, 8, and 15) and carboplatin (AUC 6 mg/mL per minute on day 1) in a 21-day cycle	244	<80% vs. ≥80%
Denduluri 2018 [5]	Ovarian	Paclitaxel/carboplatin	Carboplatin/paclitaxel every 3 weeks: 5 AUC/175 mg/m^2	170	<85% vs. ≥85%
Au-Yeung 2014 [28]	Ovarian	Paclitaxel/carboplatin	Carboplatin AUC 5–6, paclitaxel 175 mg/m^2	537	<85% vs. ≥85%
Crawford 2020 [29]	NSCLC	Platinum-based therapies: carboplatin/paclitaxel, pemetrexed/carboplatin, carboplatin/bevacizumab/ paclitaxel, pemetrexed/ cisplatin, carboplatin/ pemetrexed/bevacizumab, carboplatin/gemcitabine	Carboplatin + paclitaxel 5 AUC/175 mg/m^2; Carboplatin + pemetrexed 5 AUC/500 mg/m^2; Carboplatin + bevacizumab + paclitaxel 5 AUC/15 mg/kg/175 mg/ m^2; Pemetrexed + cisplatin 500 mg/m^2/75 mg/m^2; Carboplatin + pemetrexed + bevacizumab 5 AUC/500 mg/m^2/15 mg/kg; Carboplatin + gemcitabine 5 AUC/ 1,000 mg/m^2 × 2 (days 1 and 8)	3,866	<85% vs. ≥85%
Denduluri 2018 [5]	Breast	The most common chemotherapy regimens were paclitaxel/ bevacizumab q4w, albumin-bound paclitaxel q3w, and weekly paclitaxel	Paclitaxel/bevacizumab every 4 weeks 240 mg/m^2/30 mg/kg, six cycles; Albumin-bound paclitaxel every 3 weeks 300 mg/m^2, six cycles; Paclitaxel weekly 80 mg/m^2, 25 cycles; Docetaxel every 3 weeks 75 mg/m^2, eight cycles; Carboplatin/paclitaxel every 3 weeks 6 AUC/175 mg/m^2, eight cycles; Vinorelbine weekly 25 mg/m^2, 25 cycles; Carboplatin/paclitaxel every 4 weeks 6 AUC/240 mg/m^2, six cycles	874	<85% vs. ≥85%
Studies evaluating FOLFOX, FOLFIRI, or FOLFIRINOX regimens in colorectal or pancreatic cancer					
Nakayama 2014 [25]		FOLFIRI	Irinotecan (150 mg/m^2) and folinic acid (200 mg/m^2) followed by a bolus infusion of fluorouracil (400 mg/m^2) and subsequent continuous infusion of fluorouracil (2,400 mg/m^2), repeated every 2 weeks until disease progression	36	<80% vs. ≥80%
	Colorectal	mFOLFOX6	Six cycles of mFOLFOX6, consisting of oxaliplatin (85 mg/m^2) and folinic acid (200 mg/m^2), followed by a bolus infusion of fluorouracil (400 mg/m^2) and subsequent continuous infusion of fluorouracil (2,400 mg/m^2), repeated every 2 weeks followed by maintenance therapy with oral S-1. Reintroduction of mFOLFOX6 therapy was scheduled after four cycles of S-1 or upon tumor progression	30	<79% vs. ≥79%
Kobayashi 2019 [24]	Pancreas	FOLFIRINOX	Irinotecan: 180 mg/m^2; oxaliplatin: 85 mg/m^2; 5-FU bolus: 400 mg/m^2; 5-FU continuous infusion: 2,400 mg/m^2	359	Irinotecan: <75% vs. ≥75% Oxaliplatin: <70% vs. ≥75% 5-FU bolus: 0% vs. >0% 5-FU continuous infusion: <80% vs. ≥80%
Lee 2017 [26]	Pancreas	FOLFIRINOX	85 mg/m^2 for oxaliplatin; 180 mg/m^2 for irinotecan; 400 mg/m^2 for 5-FU as a bolus and 2,400 mg/m^2 for 5-FU via continuous infusion every 2 weeks	133	<80% vs. ≥80%

AUC, area under the curve; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; FOLFOX, folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin; FOLIRINOX, folinic acid (leucovorin), fluorouracil (5-FU), irinotecan, and oxaliplatin; mFOLFOX6, modified FOLFOX (six cycles postoperative); FU, fluorouracil; NSCLC, non-small cell lung cancer; q3w, every 3 weeks; q4w, every 4 weeks; RDI, relative dose intensity.

CRC or pancreatic cancer. Five estimates from four studies were included in the meta-analysis for OS of carboplatin-based regimens for ovarian, NSCLC, or breast cancer [5, 28, 29, 33] (Fig. 4). The summary HR was 1.17 (95% CI: 1.07–1.27), demonstrating a significant increased risk of mortality for RDI levels <80% versus ≥80% or < 85% versus ≥85%. No significant heterogeneity was present in this analysis, with HRs ranging from 1.14 (95% CI: 0.71–1.81) for paclitaxel and carboplatin in ovarian cancer in a study of Japanese patients [33] to 1.22 (95% CI: 0.77–1.94) for the same combination and tumor type in a study of American patients [5]. Four estimates from three studies were included in the meta-analysis for OS of FOLFOX-, FOLFIRI-, or FOLFIRINOX-based regimens for CRC or pancreatic cancer [24–26] (Fig. 4). The summary HR was 1.39 (95% CI: 1.03–1.89), demonstrating a significant increased risk of mortality at RDI levels <80% versus ≥80% or < 85% versus ≥85%. Results were somewhat heterogeneous ($I^2 = 57\%$; $p = .07$), with HRs ranging from 0.90 (0.41–2.21) for oxaliplatin RDI <79% in the mFOLFOX6 regimen [25] to 2.72 (1.22–6.04) for irinotecan RDI <80% in the FOLFIRI regimen [25].

Risk of Bias Assessment

Risk of bias could not be evaluated in one study of pooled data from clinical trials because of insufficient information about the design of the original studies [25]. Among the 21 cohort studies, the score for the Newcastle-Ottawa Scale assessments ranged from 3 to 8 with a median score of 6 out of a possible 9. The most frequent reasons for losing points on the risk of bias assessment included not describing the nonexposed cohort (typically because nonexposed cohorts were excluded from the study), having <1 year of follow-up, and not controlling for tumor stage or other additional factors. However, this apparent deficit was mitigated by restricting cohorts to specific tumor stages in these studies (thus obviating the need for tumor stage adjustment in the analyses). Therefore, confounding by disease stage was addressed for all included studies. Another concern was that several studies did not report whether follow-up time was sufficient to observe the survival outcomes of interest. This deficit may affect the precision of HR and survival time estimates in observational studies. Other factors evaluated in the risk of bias analysis related to ascertainment of exposure and outcomes and comparability of the exposure groups, which were well defined in nearly all studies. Overall, the risk of bias related to the outcomes of interest was generally low in the included observational studies. The Cochrane Risk of Bias assessment was conducted on the clinical trial included and had insufficient information reported in the trial to confirm a low risk of bias [21].

Safety Assessments

Grade 3 or higher hematologic toxicities were reported by 10 studies (two with age stratification) [16, 18, 20, 26, 27, 29, 30, 33] (Fig. 5). The cumulative incidence of grade 3 or higher hematologic toxicities was higher for carboplatin-based regimens than FOLFOX- or FOLFIRI-based regimens (thrombocytopenia: 14%–22% vs. 1%–4%; anemia: 15%–19% vs. 5%–19%; neutropenia: 24%–58% vs. 19%–47%).

Discussion

This systematic literature review and meta-analysis identified 22 published scientific studies evaluating the impact of RDI on survival outcomes in patients with solid tumors from 2013 to 2020. The need to group studies by diverse tumor types, treatment regimens, and different RDI levels reduced the number within each classification and made meta-analysis infeasible for most studies. However, in two categories of studies—four carboplatin-based and three FOLFOX-, FOLFIRI-, or FOLFIRINOX-based—meta-analysis evaluation was feasible, and the association between low RDI and poor OS was consistent.

The results of the meta-analysis showed a significant risk of increased mortality among patients with cancer treated with carboplatin-based or FOLFOX- or FOLFIRI-based regimens at RDI <80% or <85% compared with those treated at RDI ≥80% or ≥85%%. These results are consistent with those reported in the review by Havrilesky et al., in which patients with advanced or metastatic lung, breast, or ovarian cancer treated with chemotherapy had favorable survival with an RDI ≥85% [1].

The effect of RDI on survival may be confounded by other prognostic factors like age, body composition, comorbidities, and chemotherapy-induced toxicities. Body composition was found to be a major determinant of chemotherapy tolerance and adherence [37] with greater visceral and intramuscular adiposity increasing the risk of delivering less than the planned dose of chemotherapy, thereby reducing the efficacy of chemotherapy. Feliciano et al. reported a 30% increase in risk of death with low RDI among patients with breast cancer and obesity [37]. Another study demonstrated a positive correlation between obesity and reduced dose intensity of carboplatin, which negatively impacted PFS in patients with advanced serous ovarian cancer [28]. Another prognostic factor, age, was not found to affect RDI similarly, with the same chemotherapy efficacy observed for elderly and nonelderly patients with cancer [5, 38]. However, elderly patients are at increased risk of chemotherapy-induced toxicities like febrile neutropenia and asthenia, which often lead to lowering of RDI and reduced treatment efficacy [38].

The inclusion of various therapeutic constituents in the regimens studied may have introduced heterogeneity in the effects of RDI on survival. For example, of the five studies of carboplatin-based regimens, two also included bevacizumab, which may have influenced survival. A study of the addition of bevacizumab to mFOLFOX6 provided evidence that the combination allows a lower RDI of mFOLFOX6 to achieve equivalent survival times compared with higher RDI without bevacizumab [22]. However, in the studies included in the meta-analyses, there was no evidence that constituents were added depending on RDI threshold; therefore, the additional constituents are unlikely to be confounders of the summary RDI-survival associations observed.

In the current study, grade 3 or higher neutropenia had the highest cumulative incidence among hematologic toxicities, whereas anemia and thrombocytopenia occurred at similar frequencies. Febrile neutropenia, a complication of significant neutropenia, is considered a medical emergency with a risk of mortality requiring immediate hospitalization that may result in delays and/or reductions to planned

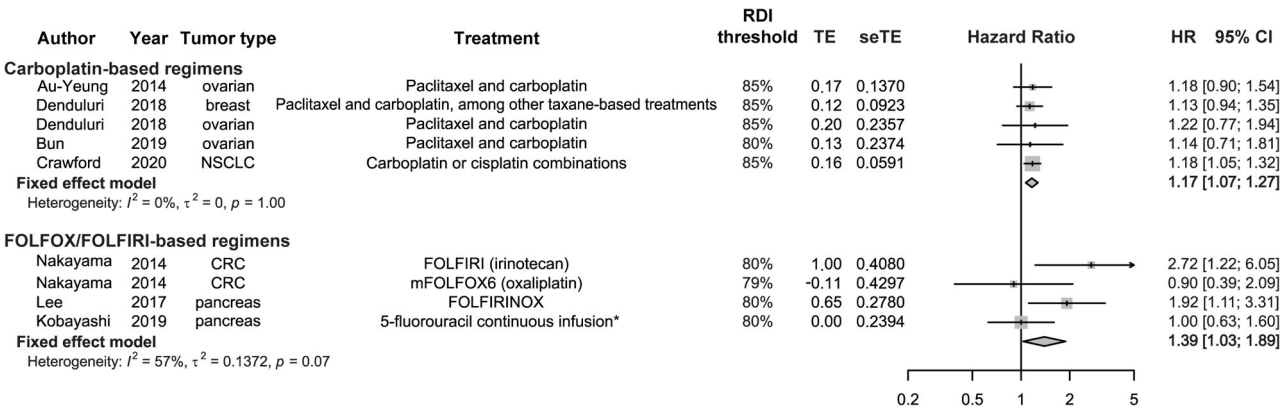

Figure 4. Association of RDI with OS in studies of FOLFOX-, FOLFIRI-, or FOLFIRINOX-based and carboplatin-based regimens. *, Kobayashi et al. (2019) evaluated 5-flurouracil infusion as part of an evaluation of constituents of FOLFIRINOX.
Abbreviations: CI, confidence interval; CRC, colorectal cancer; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; FOLIRINOX, folinic acid (leucovorin), fluorouracil (5-FU), irinotecan, and oxaliplatin; HR, hazard ratio; mFOLFOX6, modified folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin (six cycles postoperative); NSCLC, non-small cell lung cancer; OS, overall survival; RDI, relative dose intensity; seTE, standard error of treatment effect; TE, treatment effect.

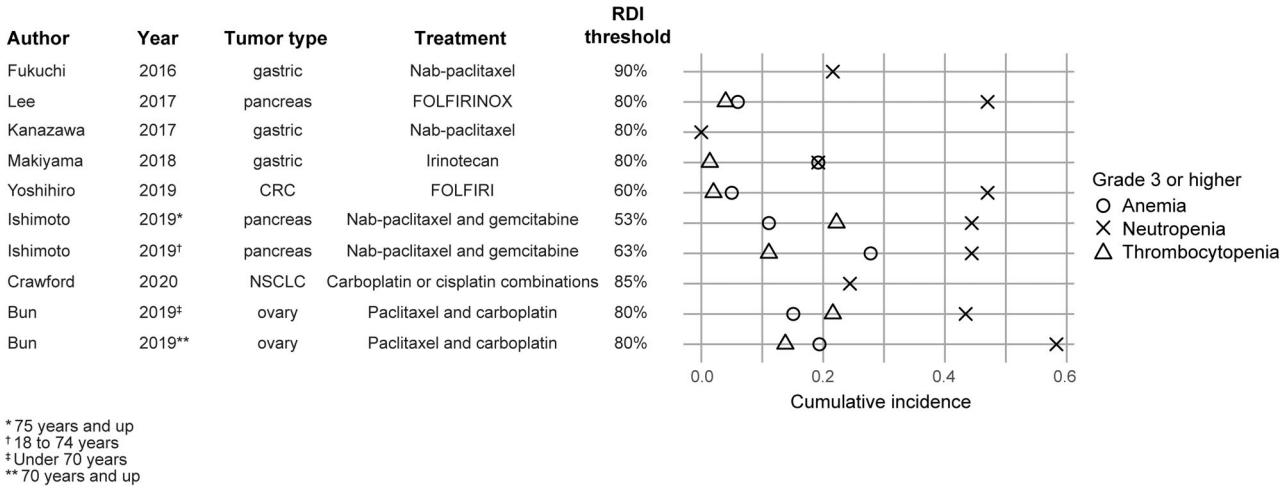

Figure 5. Cumulative incidence of grade 3 or higher hematologic toxicities in studies that reported RDI and survival associations.
Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; FOLIRINOX, folinic acid (leucovorin), fluorouracil (5-FU), irinotecan, and oxaliplatin; NSCLC, non-small cell lung cancer; RDI, relative dose intensity.

chemotherapy [39]. Primary prophylaxis with granulocyte-colony stimulating factors may improve patient outcomes by reducing the depth and duration of neutropenia, thereby reducing the risk of febrile neutropenia and helping to maintain planned chemotherapy dose intensity [39].

Chemotherapy-induced thrombocytopenia may also result in reduced RDI and treatment delays and/or reductions [40]. Studies have indicated the highest prevalence of thrombocytopenia in patients with solid tumors with CRC, NSCLC, and ovarian cancer [40, 41] and with platinum-based and gemcitabine-based chemotherapy regimens [42, 43]. Several therapies, including thrombopoietin receptor agonists romiplostim and eltrombopag, have been shown to be effective in correcting platelet counts [43–46]. Suppression of hematopoiesis is a common adverse effect of chemotherapy, resulting in hematologic toxicities that eventually lead to delay or reduction of cancer therapy because of inadequate blood counts [47]. Thus, the results from the current study as well as earlier studies suggest that maintaining RDI while preventing neutropenia and managing other hematologic toxicities may ultimately benefit OS.

There are several limitations to this systematic review. Although each study addressed potential confounding by including only advanced or metastatic disease and/or by statistical adjustment for stage, additional disease severity, or comorbidity, some of the association between lower RDI and survival may still be attributed to confounding factors like worse performance status. Additionally, most of the studies included in this review were retrospective, observational studies based in clinical or institutional patient populations, and variations in clinical practice likely influenced which patients received high versus low RDI regimens. Generalizability may also be influenced by the geographic representation of the studies published. Many of the studies identified in the literature review and three of the nine studies included for meta-analysis were from

Japan, with studies from the U.S., Australia, and South Korea also contributing. A lack of published evidence from other regions limits generalizability, and publication bias may have resulted in fewer studies with findings of no RDI-survival association being available in the literature. The clinical trial [21] was adjudicated to have "some concerns" per the Cochrane Risk of Bias scale. For example, the randomization method was not reported, and it was unclear whether patients were aware of their regimen assignment, which influenced the bias score.

The results of the systematic literature review were also limited by demographic and baseline characteristics; chemotherapy treatment patterns and management of toxicities may differ in other regions or patient populations. Because meta-analyses were conducted only with studies or estimates reporting similar RDI levels per category for tumor types and chemotherapy regimens, the results for the meta-analyses were only generalizable to those study populations. We identified several studies that reported median OS and/or PFS times stratified by RDI level; however, statistical comparisons were not always reported, and those that were reported were usually unadjusted for potential confounding factors. Although those studies were not included in the meta-analyses, we presented their results graphically as supporting evidence of the RDI association with longer survival times. Furthermore, many publications did not describe the method of RDI calculation, whereas others did not define any specific RDI threshold but instead compared high and low dose regimens, which impacted the ability to evaluate the association between RDI and survival outcomes. A standardization of the RDI calculation and of its reporting is needed to determine the impact of maintaining planned dose intensity on the outcomes in patients with advanced solid tumors [1]. Moreover, predicting an RDI decrease before treatment initiation or during treatment is difficult, despite potential planned dose delays or reductions unrelated to chemotherapy-induced toxicity.

Conclusion

This review and meta-analysis summarized recent evidence and quantified the effect of RDI on survival outcomes. Although multiple factors contribute to reductions in RDI, hematologic toxicities are common and may be preventable. As cancer therapy evolves, ongoing research can continue to elucidate the associations between RDI, dose delays and reductions, and survival outcomes in patients with solid tumor cancer.

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Disclosures

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