European Journal of Surgical Oncology 45 (2019) 1432–1438

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Neoadjuvant vs. adjuvant chemotherapy for cholangiocarcinoma: A propensity score matched analysis☆

Siddhartha Yadav [a], Hao Xie [a], Irbaz Bin-Riaz [a], Prabin Sharma [b], Urshila Durani [a], Gaurav Goyal [a], Bijan Borah [c], Mitesh J. Borad [d], Rory L. Smoot [e], Lewis R. Roberts [f], Ronald S. Go [g], Robert R. McWilliams [a], Amit Mahipal [a, *]

[a] Department of Oncology, Mayo Clinic, Rochester, MN, 55905, USA
[b] Department of Gastroenterology, Yale New Haven Health – Bridgeport Hospital, Bridgeport, CT, 06610, USA
[c] Robert D. and Patricia E. Kern Mayo Clinic Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, 55905, USA
[d] Division of Hematology/Oncology, Department of Medicine, Mayo Clinic, Scottsdale, AZ, 85259, USA
[e] Division of Hepatobiliary and Pancreas Surgery, Department of Surgery, Mayo Clinic, Rochester, MN, 55905, USA
[f] Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, 55905, USA
[g] Division of Hematology, Mayo Clinic, Rochester, MN, 55905, USA

ARTICLE INFO

Article history:
Received 3 January 2019
Received in revised form
1 March 2019
Accepted 16 March 2019
Available online 21 March 2019

Keywords:
Chemotherapy
Neoadjuvant
Cholangiocarcinoma
Adjuvant
Surgery
Survival

ABSTRACT

Background: Chemotherapy is frequently used in cholangiocarcinoma as an adjunct to surgical resection, but the appropriate sequence of chemotherapy with surgery is unclear.
Patients and methods: Using the National Cancer Database, we identified patients who underwent surgery and chemotherapy for stage I-III cholangiocarcinoma between 2006 and 2014. The propensity score reflecting the probability of receiving neoadjuvant chemotherapy was estimated by multivariate logistic regression method. Patients in the neoadjuvant and adjuvant chemotherapy study arms were then propensity-matched in 1:3 ratios using the nearest neighbor method. Overall Survival (OS) in the matched data set was estimated using the Kaplan-Meier method. Hazard ratios (HRs) were calculated using Cox proportional hazard regression model.
Results: Of the 1450 patients who met our inclusion criteria, 299 (20.6%) received neoadjuvant chemotherapy while 1151 (79.3%) received adjuvant chemotherapy. The median age at diagnosis was 63 years. 278 patients in the neoadjuvant group were matched to 700 patients in the adjuvant group. In the matched cohort, patients who received neoadjuvant chemotherapy had a superior OS compared to those who received adjuvant chemotherapy (Median OS: 40.3 vs. 32.8 months; HR: 0.78; 95% CI: 0.64–0.94, $p = 0.01$). The 1- and 5-year OS rates for the neoadjuvant chemotherapy group were 85.8% and 42.5% respectively compared to 84.6% and 31.7% for the adjuvant chemotherapy group.
Conclusion: In this large national database study, neoadjuvant chemotherapy was associated with a longer OS in a select group of patients with cholangiocarcinoma compared to those who underwent upfront surgical resection followed by adjuvant chemotherapy.

Introduction

Cholangiocarcinoma is a rare and aggressive cancer of the biliary epithelium. Approximately 8000 people in the United States are diagnosed with cholangiocarcinoma each year [1]. Surgical resection with histologically negative margin is the only potentially curative treatment for cholangiocarcinoma. However, a majority of the patients are not amenable for surgical resection as they present with locally advanced disease or distant metastasis [2]. Even in

Abbreviations: HR, hazard ratio; NCDB, national cancer database; OS, Overall Survival.

☆ This study had been deemed IRB exempt.

* Corresponding author. Division of Medical Oncology, 200 First Street SW, Rochester, MN, 55905, USA.
E-mail address: Mahipal.Amit@mayo.edu (A. Mahipal).

https://doi.org/10.1016/j.ejso.2019.03.023
0748-7983/

cases that are surgically resected, recurrences develop in approximately two-thirds of cases, and overall survival (OS) is poor [3–5].

Several chemotherapy regimens have been explored in the adjuvant setting, and many retrospective studies evaluating these have shown improvement in outcomes [6–12]. These results have led to randomized clinical trials of adjuvant chemotherapy, but a definitive survival advantage has been difficult to prove [13–16]. Most recently, the BILCAP study, which randomized patients to receive adjuvant capecitabine or placebo, showed improvement in OS in the per-protocol analysis, although this was not evident in the intention-to-treat analysis [17]. In the absence of definitive evidence, the decision on adjuvant chemotherapy has been left to clinicians and patients, and chemotherapy is frequently being used in these cases.

Neoadjuvant chemotherapy may be of benefit in these patients by improving resectability similar to other malignancies including pancreatic cancer and breast cancer. Neoadjuvant chemotherapy may also allow for better selection of patients for surgical resection by excluding patients who develop metastatic disease and sparing them from unnecessary surgery. This question has only been explored in small retrospective series of patients, but some of these studies have shown some promising results [18–22]. It is unclear how this strategy compares to adjuvant chemotherapy, as they have not been compared in prospective or retrospective studies. In

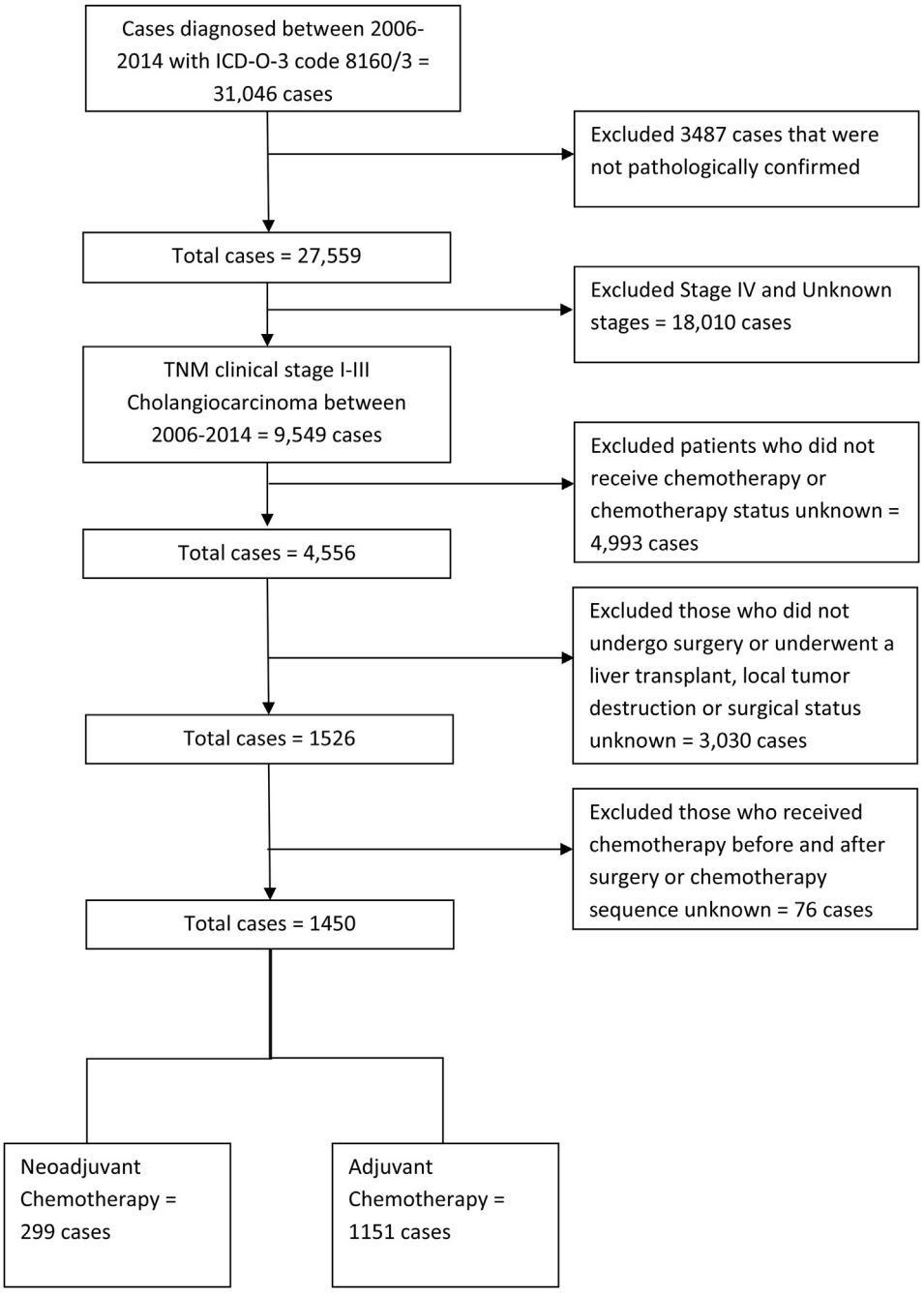

Fig. 1. Patient selection schema.

this study utilizing the National Cancer Database (NCDB), we evaluate the role of neoadjuvant chemotherapy in OS of patients with cholangiocarcinoma.

Materials and methods

Patient selection

We identified patients in NCDB using the histologic code for cholangiocarcinoma (8160/3) per the third edition of the International Classification of Diseases for Oncology. We restricted our analysis to patients who had the diagnosis confirmed by histology or cytology and were diagnosed between the years 2006 and 2014. Patients with metastatic disease or unknown stage at diagnosis were excluded. In addition, we excluded patients who did not undergo surgery, did not receive chemotherapy, underwent liver transplant or if the sequence of chemotherapy in relation to surgery was unknown (Fig. 1).

We abstracted data on demographics, tumor characteristics, treatment modalities, and OS. The primary outcome of this study was to evaluate the difference in OS between patients who received neoadjuvant chemotherapy and adjuvant chemotherapy.

Propensity score matching

We estimated the propensity score or the probability of receiving neoadjuvant chemotherapy by using a multivariable logistic regression model. Covariates included in the model were age at diagnosis, sex, race, insurance status, Charlson comorbidity score, year of diagnosis, facility type, tumor location, tumor grade, clinical stage, and use of radiation. Each sub-category was entered as a separate variable in the model. A 1:3 matching was then performed by using the nearest neighbor method with a caliper width equal to 0.25 standard deviations using the MatchIt' package in R [23]. We examined the balance in the baseline covariates in the matched data by using standardized mean differences (Table 1), histogram (Supplemental Figure 1) and jitter plots (Supplemental Figure 2).

Table 1
Baseline characteristics in the matched and unmatched groups.

	All Patients (N = 1450)				Matched Cohort (N = 978)			
	Neoadjuvant (N = 299)	Adjuvant (N = 1151)	Sdiff	p-value	Neoadjuvant (N = 278)	Adjuvant (N = 700)	Sdiff	p-value
Age			0.33	**<0.001**				**0.25**
18–54	105 (35.1%)	264 (22.9%)	0.27	<0.05	89 (32.0%)	193 (27.6%)	0.09	NS
55–64	97 (32.4%)	358 (31.1%)	0.02	NS	94 (33.8%)	222 (31.7%)	0.04	NS
65–74	75 (25.1%)	369 (32.1%)	0.15	<0.05	73 (26.3%)	212 (30.3%)	0.09	NS
75+	22 (7.4%)	160 (13.9%)	0.21	<0.05	22 (7.9%)	73 (10.4%)	0.02	NS
Sex				**0.92**				**0.73**
Male	156 (52.2%)	604 (52.5%)	0.00	NS	140 (50.4%)	361 (51.6%)	0.02	NS
Female	143 (47.8%)	547 (47.5%)	0.00	NS	138 (49.6%)	339 (48.4%)	0.02	NS
Race				**0.03**				**0.80**
White	273 (91.3%)	989 (85.9%)	0.17	<0.05	253 (91.0%)	630 (90.0%)	0.03	NS
Black	15 (5.0%)	76 (6.6%)	0.06	NS	14 (5.0%)	43 (6.1%)	0.04	NS
Other or unknown	11 (3.7%)	86 (7.5%)	0.16	<0.05	11 (4.0%)	27 (3.9%)	0.00	NS
Insurance Status				**0.45**				**0.72**
No insurance	6 (2.0%)	18 (1.6%)	0.03	NS	6 (2.2%)	10 (1.4%)	0.05	NS
Private	162 (54.2%)	588 (51.1%)	0.06	NS	151 (54.3%)	365 (52.1%)	0.04	NS
Government	123 (41.1%)	524 (45.5%)	0.08	NS	116 (41.7%)	314 (44.9%)	0.06	NS
Unknown	8 (2.7%)	21 (1.8%)	0.05	NS	5 (1.8%)	11 (1.6%)	0.01	NS
Charlson Score				**0.38**				**0.82**
0–1	277 (92.6%)	1082 (94.0%)	0.05	NS	257 (92.4%)	650 (92.9%)	0.01	NS
2 or higher	22 (7.4%)	69 (6.0%)	0.05	NS	21 (7.6%)	50 (7.1%)	0.01	NS
Year of diagnosis				**0.03**				**0.83**
2006–2008	55 (18.4%)	239 (20.8%)	0.06	NS	54 (19.4%)	138 (19.7%)	0.00	NS
2009–2011	100 (33.4%)	454 (39.4%)	0.12	NS	94 (33.8%)	249 (35.6%)	0.03	NS
2012–2014	144 (48.2%)	458 (39.8%)	0.16	<0.05	130 (46.8%)	313 (44.7%)	0.04	NS
Facility type				**<0.001**				**0.23**
Non-academic	92 (30.8%)	427 (37.1%)	0.13	<0.05	88 (31.7%)	245 (35.0%)	0.07	NS
Academic/Research	185 (61.9%)	685 (59.5%)	0.04	NS	171 (61.5%)	424 (60.6%)	0.02	NS
Other/unknown	22 (7.4%)	39 (3.4%)	0.17	<0.05	19 (6.8%)	31 (4.4%)	0.10	NS
Location				**<0.001**				**0.43**
Intrahepatic	222 (74.2%)	620 (53.9%)	0.43	<0.05	203 (73.0%)	487 (69.6%)	0.07	NS
Extrahepatic	74 (24.7%)	486 (42.2%)	0.37	<0.05	72 (25.9%)	208 (29.7%)	0.08	NS
Not specified/unknown	3 (1.0%)	45 (3.9%)	0.18	<0.05	3 (1.1%)	5 (0.7%)	0.03	NS
Grade				**<0.001**				**0.01**
1	23 (7.7%)	104 (9.0%)	0.04	NS	23 (8.3%)	63 (9.0%)	0.02	NS
2	104 (34.8%)	527 (45.8%)	0.22	<0.05	104 (37.4%)	299 (42.7%)	0.10	NS
3 or 4	65 (21.7%)	365 (31.7%)	0.22	<0.05	65 (23.4%)	192 (27.4%)	0.09	NS
Unknown	107 (35.8%)	155 (13.5%)	0.53	<0.05	86 (30.9%)	146 (20.9%)	0.23	<0.05
Clinical Stage				**0.04**				**0.96**
Stage I	136 (45.5%)	439 (38.1%)	0.14	<0.05	127 (45.7%)	313 (44.7%)	0.02	NS
Stage II	103 (34.4%)	478 (41.5%)	0.14	<0.05	96 (34.5%)	245 (35.0%)	0.01	NS
Stage III	60 (20.1%)	234 (20.3%)	0.00	NS	55 (19.8%)	142 (20.3%)	0.01	NS
Radiation				**0.59**				**0.77**
No	161 (53.8%)	618 (53.7%)	0.00	NS	156 (56.1%)	400 (57.1%)	0.02	NS
Yes	138 (46.2%)	529 (46.0%)	0.00	NS	122 (43.9%)	300 (42.9%)	0.02	NS
Unknown	0 (0.0%)	4 (0.3%)	0.08	NS	0 (0.0%)	0 (0.0%)	0.00	

NS: Not Significant.

Statistical analysis

We compared the baseline categorical variables in the matched and unmatched cohort using Chi-Square test and adjusted for p-values within each sub-group using Bonferroni correction. We estimated the OS in the matched data set using Kaplan-Meier curve and compared OS between the two groups by the log-rank test. Hazard ratios (HRs) were calculated using Cox proportional hazard regression model. All tests were two-sided. A p-value less than 0.05 was considered significant. Statistical analysis was performed using R software (version 3.5.1).

Results

Baseline characteristics and patterns of neoadjuvant chemotherapy use

A total of 1450 patients met our inclusion criteria; 299 (20.6%) received neoadjuvant chemotherapy while 1151 (79.4%) received adjuvant chemotherapy (Fig. 1). The median time from diagnosis to surgery in the neoadjuvant group was 172 days, while it was 25 days in the adjuvant group ($p < 0.001$). The median time to starting chemotherapy from diagnosis was 39 days and 84 days in neo-adjuvant and adjuvant chemotherapy groups respectively ($p < 0.001$). Clinical variables associated with higher likelihood of using of neoadjuvant chemotherapy were younger age at diagnosis, white race, year of diagnosis between 2012 and 2014, intra-hepatic location of tumor, unknown tumor grade and clinical stage I (Table 1).

Propensity score matching

From the neoadjuvant group, 278 (92.9%) patients were matched with 700 (60.8%) patients who received adjuvant chemotherapy. All covariates, except for unknown tumor grade, were adequately balanced in the matched data set as demonstrated by a standard difference of less than 0.1 (Table 1, Supplemental Figure 1 and Supplemental Figure 2).

OS in the matched data set

The median follow up duration of the matched cohort was 27 months. In the neoadjuvant chemotherapy group, 56.8% of the patients received multi-agent chemotherapy compared to 45.9% in the adjuvant chemotherapy group ($p < 0.05$), while the rest received single-agent chemotherapy. Patients who received neoadjuvant chemotherapy were more likely to have R0 surgical resection compared to patients who underwent upfront surgical resection (71.2% vs. 61.6%, $p = 0.02$). Patients who underwent neoadjuvant chemotherapy also had a significantly longer OS compared to those who received adjuvant chemotherapy (median OS: 40.3 vs. 32.8 months, HR: 0.78, 95% CI: 0.64–0.94, $p = 0.01$, Fig. 2). The 1- and 5-year OS rates for the neoadjuvant group was 85.8% and 42.5% respectively, compared to 84.6% and 31.7% for the adjuvant group.

In sub-group analysis, statistically significant longer OS for neoadjuvant chemotherapy was noted in the younger age group (18–54 years), male sex, white race, government insurance, Charlson score 1–2, year of diagnosis 2006–2008, treatment at an academic facility, intrahepatic tumor location, unknown tumor grade, and clinical stage I (Fig. 3).

Discussion

The role of neoadjuvant chemotherapy in cholangiocarcinoma has been explored in several small clinical studies and case reports with mixed results [20,24–29]. A retrospective review of 28 patients who received neoadjuvant chemotherapy did not show any difference in OS compared to patients who underwent upfront resection [24]. In a more recent study of 74 patients with unresectable intrahepatic cholangiocarcinoma, neoadjuvant chemotherapy was found to be an effective downstaging option although it was not associated with a difference in OS [20]. However, the majority of prior studies were limited by their small sample size and lack of a comparable control group, which did not allow for a meaningful evaluation of the effects of neoadjuvant chemotherapy on OS. In contrast, in our large national database study, we evaluated 278 cholangiocarcinoma patients receiving neoadjuvant

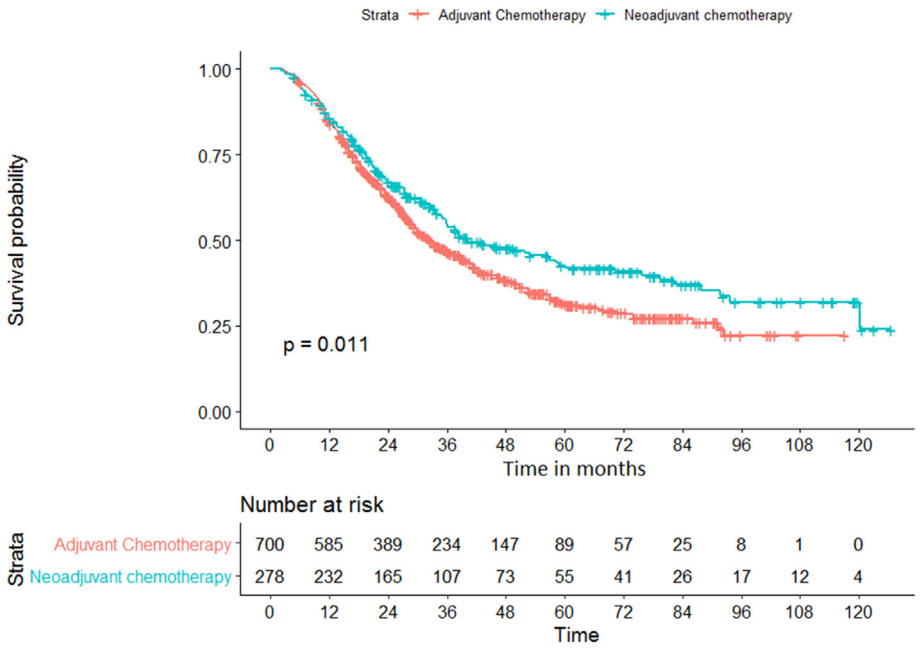

Fig. 2. Overall survival between patients who received neoadjuvant chemotherapy and adjuvant chemotherapy in the matched cohort.

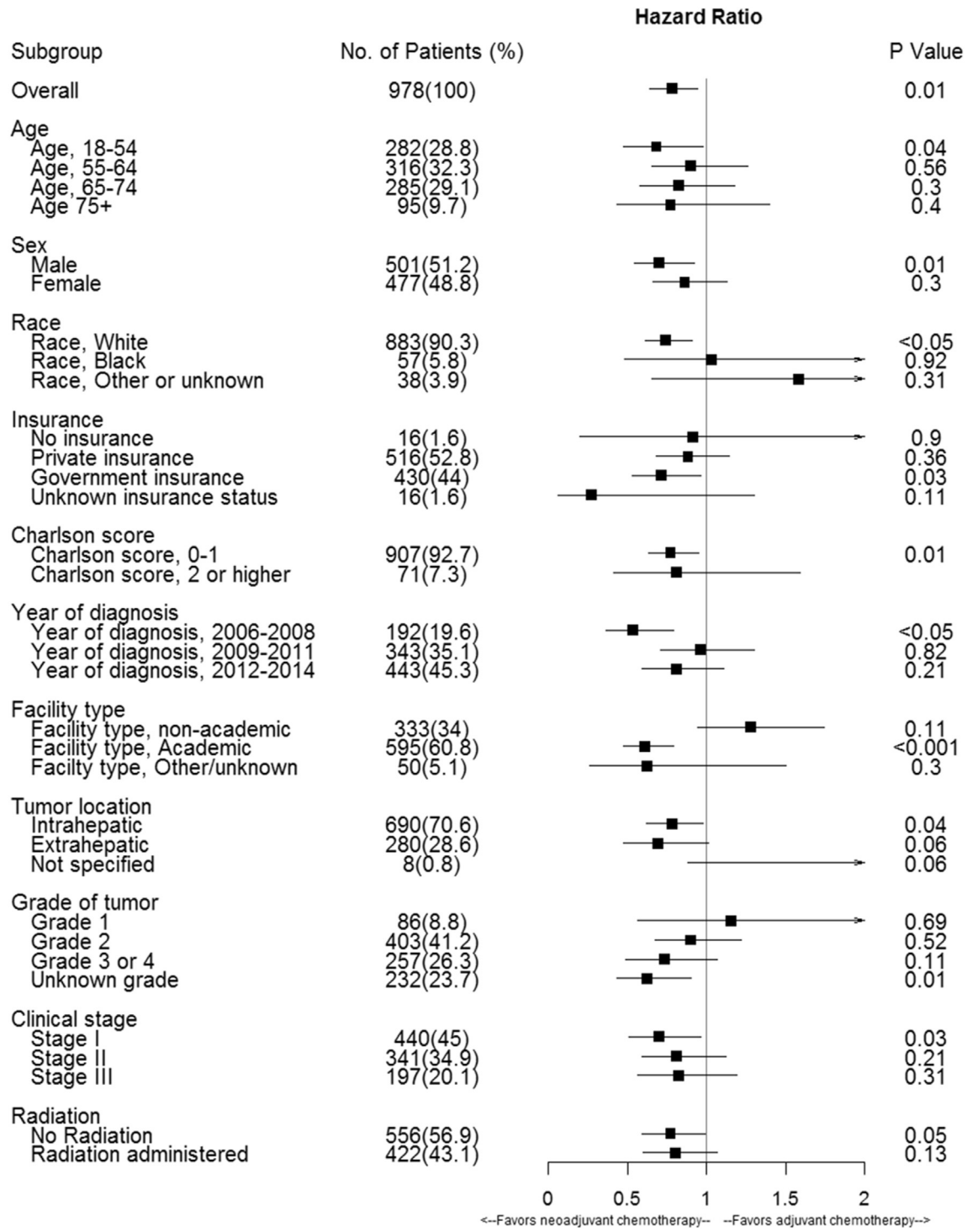

Fig. 3. Forest plot demonstrating hazard ratios for neoadjuvant chemotherapy for different subgroups in the matched cohort.

chemotherapy and found that neoadjuvant chemotherapy followed by surgery was significantly associated with longer OS in patients with cholangiocarcinoma.

There are several theoretical possibilities regarding how neoadjuvant chemotherapy can improve OS compared to adjuvant chemotherapy. First, neoadjuvant chemotherapy can downstage tumors and improve the probability of complete resection of tumors with negative margins. R0 resections are typically associated with better OS [30–32]. In our study as well, a significantly higher proportion of patients in the neoadjuvant chemotherapy had R0 resections compared to the group that underwent upfront resection despite being matched for tumor stage. Second, neoadjuvant chemotherapy potentially allows for the selection of patients who may benefit from surgical resection. Administration of neoadjuvant chemotherapy provides additional time to identify patients who have a chemotherapy-resistant micrometastatic disease and are more likely to progress to overt metastasis irrespective of surgical intervention. Third, post-surgical morbidities may preclude

administration of chemotherapy in the adjuvant chemotherapy group. In our matched cohort, multiagent chemotherapy was administered less frequently in the adjuvant chemotherapy group compared to the neoadjuvant group, which could be due to post-surgical morbidities in the adjuvant arm. However, this also raises the possibility that the adjuvant chemotherapy arm may have been undertreated.

In subgroup analysis, we identified several features of patients who may benefit from neoadjuvant chemotherapy (Fig. 3). Although this may help in selecting patients who will benefit from neoadjuvant chemotherapy approach, these results need to be interpreted with caution. Our study may not have detected difference across several subgroups due to lack of statistical power, rather than due to an absence of a real difference. Interestingly, we identified that stage I patients may be more likely to benefit from neoadjuvant chemotherapy compared to stage II-III. This challenges the traditional notion that neoadjuvant chemotherapy may be effective by facilitating surgical resectability by downstaging tumors [29] and hence should be reserved for higher stage tumors. The observed benefits in early-stage disease could be due to the effective management of micrometastatic disease rather than due to tumor downstaging. We also observed that neoadjuvant chemotherapy was associated with superior OS in patients diagnosed in the years 2006–2008 compared to later years of diagnosis, although the proportion of patient receiving neoadjuvant chemotherapy between 2006 and 2008 was lower compared to later years. The reasons behind these findings are unclear, but selection bias or a type I error due to low number of patients in this group cannot be ruled out. These findings and several other subgroup analysis findings will have to be validated in future studies.

In this study, we also included patients who received radiation in addition to chemotherapy. Neoadjuvant chemoradiation in conjunction with liver transplant has shown some benefit in cholangiocarcinoma [33–37]. However, its role in patients who are not candidates for a liver transplant is unclear. Our analysis excluded patients who underwent liver transplant. The proportion of patients who received radiation treatment was also similar between neoadjuvant and adjuvant chemotherapy groups, making it unlikely that the observed difference in survival due to neoadjuvant chemotherapy is due to the effect of radiation therapy alone.

In recent years, studies have demonstrated the effectiveness of neoadjuvant chemotherapy approach in several tumor types [38,39]. In the absence of any clinical trials addressing the role of neoadjuvant chemotherapy in cholangiocarcinoma, we designed this national database study to evaluate the efficacy of this approach. To the best of our knowledge, this is the first and the largest study that has demonstrated a survival advantage for patients who received neoadjuvant chemotherapy for cholangiocarcinoma. Our findings will need to be confirmed and validated in future prospectively-designed clinical trials such as the ongoing neoadjuvant clinical trial with the combination of gemcitabine, cisplatin, and nab-paclitaxel in patients with high-risk bile duct cancer [40].

Our study suffers from the usual limitations of the National Cancer Database [41] and retrospective analyses. In addition, we acknowledge the possibility of selection bias since we were not able to include patients who may have started with neoadjuvant chemotherapy, but did not make it to surgery due to the progression of the disease. However, this bias may not be purely detrimental, as one of the strengths of neoadjuvant chemotherapy is that it allows selection of patients who may benefit from surgery, and avoids unnecessary surgical interventions in those who may not. In addition, the data on the type of chemotherapy regimens, dosage and duration are not available. The adverse events from the therapies are also not recorded in NCDB. This limit our analysis in comparing therapies between the two groups and determining which regimens works best in neoadjuvant setting. All covariates were well-balanced between the matched cohorts except for unknown tumor grade. However, it is unlikely that a higher proportion of patients with an unknown grade in the neoadjuvant chemotherapy could lead to the observed differences. On further analysis, we observed that unknown grade was in-fact associated with poor prognosis. The higher proportion of unknown grade tumors in the neoadjuvant chemotherapy is likely a result of neoadjuvant chemotherapy causing a significant pathological response in the tumor leading to a difficulty in proper classification of tumor grade.

Conclusions

In this large national database study, we have demonstrated that neoadjuvant chemotherapy followed by surgery is associated with better OS in patients with cholangiocarcinoma compared to upfront resection followed by adjuvant chemotherapy. Our findings have implications in designing future clinical trials for generating definitive evidence on the comparative benefit of neoadjuvant chemotherapy in managing patients with cholangiocarcinoma.

Declaration of interest

RRM serves on the advisory board for Ipsen, steering board for BMS and has received institutional support from Merck and BMS. RLS serves in consulting/advisory role for Intuitive Surgical. SY, HX, IB, PS, UD, GG, BB, RSG and AM have no potential conflicts of interest to declare.

Prior presentation

This study was presented in part as a poster presentation at the 2018 European Society of Medical Oncology Annual Congress in Munich, Germany.

Acknowledgements

None.

Appendix ASupplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2019.03.023.

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