Survival Benefits of Chemotherapy, Radiotherapy, and Chemoradiotherapy in Patients with Unresectable Intrahepatic Cholangiocarcinoma: A Population-Based Study

Keywords
radiotherapy, chemoradiotherapy, SEER, chemotherapy, Unresectable intrahepatic cholangiocarcinoma

Abstract

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Methods: We utilized the Surveillance, Epidemiology, and End Results (SEER) database's SEER*stat software (version 8.3.5) to gather patient data diagnosed with unresectable ICC from 2000 to 2018. Survival curves were plotted using the Kaplan-Meier method, comparing the overall survival (OS) and cancer-specific survival (CSS) among patients who underwent radiotherapy, chemotherapy, chemoradiotherapy, or no therapy at all. Univariate and multivariate Cox regression models were employed to analyze the prognostic factors affecting these unresectable ICC patients.

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Keywords： Unresectable intrahepatic cholangiocarcinoma; chemotherapy; radiotherapy; chemoradiotherapy; SEER

Introduction

Intrahepatic cholangiocarcinoma (ICC), the second most common primary malignant tumor of the liver, originates from the intrahepatic bile duct's epithelium[1]. Over the last four decades, both the incidence and mortality rates of ICC have witnessed a steady rise[2]. Currently, curative surgical resection is largely perceived as the sole method for curing ICC[3]. Yet, owing to the concealed clinical symptoms of ICC coupled with the absence of effective early screening techniques, only a limited 20%-30% of ICC patients are eligible for curative surgical resection[4]. For patients with unresectable ICC, palliative treatment options available in clinical practice include chemotherapy (CT), radiotherapy (RT), and chemoradiotherapy[5-8]. Nevertheless, the relatively small number of ICC patients and the consequent lack of extensive research data pose a significant challenge. Many existing studies are characterized by their small scale, retrospective nature, non-randomized design, and some even include mixed studies featuring gallbladder and other bile duct tumors, thereby complicating the evaluation of the therapeutic value of palliative treatment for ICC[9].

The SEER database, covering cancer incidence, treatment methods, survival rates, etc., for about 30% of the U.S. population, can serve as a valuable resource for research on rare diseases like ICC that lack randomized controlled data[10,11]. Recognizing the dearth of extensive comparative studies on palliative treatment methods for ICC, this study leverages the SEER database to evaluate the survival benefits of different clinical management methods (such as chemotherapy, radiotherapy, chemoradiotherapy, and scenarios with no chemotherapy or radiotherapy) for patients with unresectable ICC.

Materials and Methods

1.1 Ethics Statement

This study leverages the publicly available SEER database, for which we have obtained permission from the National Cancer Institute for research purposes. As the study does not involve human interaction nor the use of personal identifying information, informed consent is not required. Given that the patient data from the database has already been de-identified and made available for research, the Ethics Committee of Jiangyin People's Hospital granted an exemption for ethical approval for this study.

1.2 Search Strategy and Patient Cohort

The Surveillance, Epidemiology and End Results (SEER) program's official software, SEER*Stat

(version 8.3.5), was utilized to select patient information related to confirmed diagnoses of ICC from the SEER database for the years 2000 through 2018. Ultimately, data from 11,753 ICC patients who met the criteria was obtained. The third edition of the International Classification of Diseases for Oncology (ICD-O-3) was used to identify ICC patients. ICC patients were selected based on ICD-O-3 site codes C22.1 (intrahepatic bile duct) or C22.0 (liver). ICD-O-3 histology codes 8010, 8020, 8040, 8070, 8041, 8140, 8144, 8160, 8161, 8162, 8163, 8260, 8310, 8480, 8490, and 8560 were used to identify ICC patients. Klatskin tumors, classified as extrahepatic tumors, were excluded from this study. Other exclusions were patients diagnosed through autopsy or death certificate, those with missing or unclear causes of death, patients diagnosed within one month prior to death, patients who underwent surgical treatment, patients with concurrent primary tumors, and those lacking detailed survival data. The specific selection process and criteria are detailed in Figure 1. The data extracted included information on patients' year of diagnosis, age at diagnosis, gender, race, marital status, grade classification, tumor diameter, treatment modality (radiotherapy, chemotherapy, radiotherapy + chemotherapy, etc.), cause of death, survival time, and survival status. The study defined overall survival (OS) as the time from initial treatment to death for any reason or the end of follow-up, and cancer-specific survival (CSS) as the time from initial treatment to death due to ICC or the end of follow-up. The follow-up end date was December 2018.

1.3 Statistical Methods

OS and CSS were regarded as the primary outcome measures for this study. Categorical variables were represented by frequencies (percentages) and compared using the $\chi 2$ test. Survival curves were plotted using the Kaplan-Meier method, and survival differences were compared using the log-rank test. To identify potential prognostic factors, Cox univariate analysis was initially employed, followed by the inclusion of variables with a P-value < 0.05 in the Cox multivariate analysis. The results were presented as hazard ratios (HR) with their corresponding 95% confidence intervals (CI). The significance level (α) for testing was set at 0.05. All analyses were conducted using R software, version 4.3.0.

Results

2.1 Demographic Characteristics

The criteria detailed in the methods section led to the identification of 11,753 cases of advanced unresectable ICC from the SEER database, spanning the years 2000 to 2018. A majority of these

patients, 60.2%, were diagnosed between 2010 and 2018, compared to 39.8% diagnosed from 2000 to 2009. Concerning age distribution, 60.8% of patients were over 65, while the remaining 39.2% were under 65. The gender split was relatively even, with males accounting for 51.7% and females 48.3%. In terms of ethnicity, 77.3% were Caucasian and 22.7% were non-Caucasian. When examining marital status, we found that 54.3% of patients were married, whereas 41.7% were either unmarried or divorced. A significant number of cases, 94.5% (11109 out of total), unfortunately resulted in the patient's demise. Regarding treatment strategies for advanced unresectable ICC, 38.5% (4531 cases) received chemotherapy alone (CT Alone), 4.1% (482 cases) received radiotherapy alone (RT Alone), 8.5% (996 cases) underwent combined chemotherapy and radiotherapy (CT+RT), and 48.9% (5744 cases) did not receive either treatment (NCT+NRT). Table 1 provides a detailed breakdown of these baseline characteristics.

2.2 Survival analysis

The survival analysis revealed that patients receiving combined chemotherapy and radiotherapy had a median OS of 12.00 months (95% CI, 11-13), superior to patients receiving either chemotherapy alone with a median OS of 8.00 months (95% CI, 8-9), or radiotherapy alone with a median OS of 7.00 months (95% CI, 6-8). The shortest OS of 3.00 months (95% CI, 3-3) was observed among patients who didn't receive either treatment. The OS difference between the combined treatment group and the other three groups was statistically significant ($p < 0.0001$), whereas no significant difference was found between the chemotherapy alone and radiotherapy alone groups ($P > 0.05$). These OS trends are captured in the Kaplan-Meier curves in Figure 2.

The CSS analysis echoed the OS analysis results. The median CSS for combined chemotherapy and radiotherapy was 12.00 months (95% CI, 11-13), for chemotherapy alone it was 8.00 months (95% CI, 8-9), for radiotherapy alone it was 7.00 months (95% CI, 6-8), and for those not receiving either treatment, it was 3.00 months (95% CI, 3-3). The CSS of the combined treatment group was significantly superior to the other groups ($p < 0.0001$), and the comparison between the chemotherapy alone and radiotherapy alone groups showed no statistically significant difference ($P > 0.05$). Figure 3 depicts the Kaplan-Meier curves for CSS.

2.3 Univariate and Multivariate Cox Regression Analysis of OS

The univariate Cox proportional hazards regression model for OS highlighted the year of diagnosis, patient age, gender, marital status, grade classification, tumor diameter, and treatment modality

as significant prognostic factors for unresectable advanced ICC patients (P < 0.05, see Table 2 and Supplementary Figure 1). The multivariate model corroborated these results, further emphasizing patient age, gender, grade classification, tumor diameter, and treatment modality as independent prognostic factors (P < 0.05, see Table 2 and Supplementary Figure 1). The multivariate analysis unveiled the following associations: an increased risk of death with increasing age (HR, 1.204; 95% CI, 1.157-1.254, p < 0.001); a higher risk of death for male patients compared to female patients (HR, 1.117; 95% CI, 1.075-1.162, p < 0.001); an elevated risk of death for patients with Grade classification III-IV compared to those with Grade classification I-II (HR, 1.364; 95% CI, 1.273-1.462, p < 0.001). Moreover, patients with a tumor diameter $\leqslant$ 5cm experienced significantly improved survival rates compared to those with a diameter > 5cm (HR, 0.869; 95% CI, 0.816-0.925, p < 0.001). Finally, patients in the combined chemotherapy and radiotherapy group had a significantly reduced risk of death compared to the chemotherapy alone group (used as reference) (HR, 0.779; 95% CI, 0.723-0.840, p < 0.001). Compared to the chemotherapy alone group, the radiotherapy alone group did not show a significant increase in the risk of death (HR, 1.061; 95% CI, 0.960-1.174, p = 0.247), whereas patients who did not undergo either chemotherapy or radiotherapy had a significantly increased risk of death (HR, 1.785; 95% CI, 1.708 - 1.865, p < 0.001).

2.4 Univariate and Multivariate Cox Regression Analysis of CSS

The univariate and multivariate Cox proportional hazards regression models for CSS conveyed results similar to those for OS. Both models pointed to the year of diagnosis, patient age, gender, marital status, Grade classification, tumor diameter, and treatment modality as significant prognostic factors for unresectable advanced ICC patients (P < 0.05, see Table 3 and Supplementary Figure 2). The multivariate model also depicted patient age, gender, marital status, grade classification, tumor diameter, and treatment modality as independent prognostic factors (P < 0.05, see Table 3 and Supplementary Figure 2). The CSS multivariate Cox regression analysis identified several associations: an increased risk of death with increasing age (HR, 1.203; 95% CI, 1.154-1.254, p < 0.001); a higher risk of death for male patients, compared to female patients (HR, 1.112; 95% CI, 1.068-1.158, p < 0.001); a higher risk of death for patients with Grade classification III-IV, compared to those with Grade classification I-II (HR, 1.356; 95% CI, 1.263-1.456, p < 0.001). Unmarried or divorced patients also showed an increased risk of death compared to their married counterparts (HR, 1.044; 95% CI, 1.001-1.089, p = 0.044). Furthermore, patients with a tumor

diameter ⩽ 5cm had a significantly improved survival rate compared to those with a diameter > 5cm (HR, 0.861; 95% CI, 0.807-0.919, p < 0.001). Lastly, compared to the chemotherapy alone group (used as reference), patients in the combined chemotherapy and radiotherapy group exhibited a significantly reduced risk of death (HR, 0.775; 95% CI, 0.718-0.837, p < 0.001). Compared to the chemotherapy alone group, the radiotherapy alone group did not significantly increase the risk of death (HR, 1.070; 95% CI, 0.963-1.188, p = 0.207), while patients who did not receive either chemotherapy or radiotherapy had a significantly increased risk of death (HR, 1.824; 95% CI, 1.744-1.908, p < 0.001).

Discussion

Liver cancer ranks as one of the most prevalent tumors globally, with the incidence of new cases and associated deaths placing it sixth and third, respectively, among all malignant tumors[12, 13].ICC is a rare but highly invasive primary liver malignancy, responsible for 10%-15% of all primary liver cancers and approximately 10%-20% of cholangiocarcinomas[14,15]. Its prognosis is often poor, with an overall five-year survival rate of about 8%[15]. Recent years have witnessed an upward trend in both the incidence and mortality of ICC[16]. However, its rarity has limited large-scale studies, resulting in a lack of concrete treatment conclusions for ICC patients[17]. Commonly employed clinical interventions encompass chemotherapy, radiotherapy, and combination therapy, but the comparative efficacy of these treatments lacks a unified study. To fill this gap, we used the SEER database to analyze the effectiveness of several treatment methods for unresectable ICC patients. Our study encompasses 11,753 advanced unresectable ICC cases. The patients were treated with either CT Alone, RT Alone, CT+RT, or NCT+NRT. Median OS time for CT+RT patients was 12.00 months (95% CI, 11-13), for CT Alone was 8.00 months (95% CI, 8-9), for RT Alone was 7.00 months (95% CI, 6-8), and for NCT+NRT was 3 months (95% CI, 3-3). The OS for the CT+RT group was notably higher than the other groups (p < 0.0001). No statistical significance was observed between the OS of the CT Alone and RT Alone groups (P > 0.05). The lowest OS was among those who didn't receive either chemotherapy or radiotherapy (p < 0.0001). The results from the CSS survival analysis mirrored those from the OS survival analysis.

Univariate and multivariate Cox regression analyses indicated that age, gender, grade classification, tumor diameter, and treatment method were independent prognostic factors for advanced

unresectable ICC patients (P<0.05, see Table 2 and Supplementary Figure 1). An increase in age correlated with a higher risk of mortality (HR, 1.204; 95% CI, 1.157-1.254, p<0.001), which aligns with previous studies on the SEER database (18-34 years, 5-year mortality rate was 69.90%; 35-49 years, 5-year mortality rate was 77.86%; 50-64 years, 5-year mortality rate was 83.02%; ≥65 years, 5-year mortality rate was 91.41%; P<0.0001)[18]. We speculate that this could be due to a higher incidence of comorbidities and poorer PS scores among the elderly. Male patients exhibited a greater risk of mortality (HR, 1.117; 95% CI, 1.075-1.162, p<0.001). A study on the National Center for Health Statistics (NCHS) database[19] suggests that a higher mortality rate in male cholangiocarcinoma patients could be due to a higher incidence of concurrent cirrhosis and primary sclerosing cholangitis (PSC). Epidemiological data indicate a 27-fold increase in the risk of developing cholangiocarcinoma in cirrhosis patients and a 1560-fold increase in PSC patients. Additionally, men were found to have a higher risk of chronic liver disease and PSC compared to women[20-22].

Patients with a Grade III-IV classification, compared to those with Grade I-II, had a higher risk of death (HR, 1.364; 95% CI, 1.273-1.462, p<0.001), possibly due to the increased malignancy, stronger invasion, metastasis ability, and poorer tissue differentiation associated with Grade III-IV tumors.

While the 7th edition of the AJCC TNM staging system for ICC considers factors such as the number of tumors, vascular invasion, intrahepatic metastasis, and invasion of adjacent organs, it does not include tumor size. The 8th edition, however, introduces a 5cm threshold to differentiate between T1a and T1b stages[23]. Studies by Hwang et al. [24]and Spolverato et al.[25] revealed that a tumor diameter greater than 5cm was an independent risk factor for tumor recurrence and patient survival, and was significantly associated with microvascular invasion and poorer tumor differentiation. Our study found that patients with a tumor diameter of ⩽5cm had a significantly improved survival period compared to those with a diameter >5cm (HR, 0.861; 95% CI, 0.807-0.919, p<0.001), underscoring the prognostic value of tumor long diameter.

Though ICC has a relatively low incidence, most previous studies have focused on Biliary Tract Cancer (BTC), with ICC being a subtype where no specialized treatment or chemotherapy regimen currently exists. Research has suggested that combined chemotherapy regimens are the main first-line treatment for advanced BTC. The phase III RCT study ABC-02 [5]compared the efficacy of using

gemcitabine alone versus the combination of gemcitabine and cisplatin for unresectable BTC. The median survival time (MST) in the combination therapy group (n=204) was significantly better than that in the gemcitabine monotherapy group (n=206) (MST, 11.7 months vs. 8.1 months; HR, 0.64; 95% CI, 0.52–0.80, P<0.001). This study included 410 patients, of which 80 were ICC patients (19.5%). Another controlled study on BTC conducted by Okusaka[26] and colleagues in Japan reported similar results, with ICC patients accounting for approximately 33.3% (28/84). The results showed that the combination therapy group was superior to the gemcitabine monotherapy group (MST, 11.2 months vs. 7.7 months, HR, 0.69; 95% CI, 0.42-1.13, P=0.139). Another phase III randomized controlled trial involving BTC demonstrated that gemcitabine and cisplatin combined with S-1 (GCS) for unresectable BTC was superior to gemcitabine combined with cisplatin (GC) (mOS 13.5 months vs. 12.6 months; HR, 0.79; 90% CI, 0.628–0.996, P=0.046)[27]. In this study, ICC patients accounted for approximately 31.7% (78/246). For unresectable ICC patients, although chemotherapy is recommended as a first-line treatment option, its efficacy is not ideal, and therefore more effective treatment methods are still needed. For ICC patients with symptoms related to local lesions and no distant metastasis, radiotherapy serves as a local treatment option. This study included various radiotherapy methods such as external beam radiotherapy, brachytherapy, combined external beam and brachytherapy, and radioactive isotope therapy. The advent of advanced external beam radiation therapy techniques has brought about potential benefits in treating biliary tract cancer[28-30].

Stereotactic body radiation therapy (SBRT)[6], a new form of radiation therapy, uses CT imaging and synchronized respiratory tracking technology to reduce errors caused by respiratory motion. This method ensures an adequate dose to the tumor while minimizing the radiation dose to normal liver tissue, thereby maximizing anti-tumor effects and reducing adverse events. Zhang et al.[6] studied 43 patients with unresectable ICC who received SBRT. The median treatment dose was 24-50 Gy (with a median dose of 40 Gy), and the median survival time was 12 months. The 1-year, 2-year, and 3-year overall survival rates were 51.2%, 32.6%, and 23.3% respectively. Progression-free survival rates were 37.2%, 11.6%, and 4.7% respectively, highlighting the potential benefit of this treatment modality.

Brachytherapy (BT)[7], a form of radiation therapy administered at close range, is able to deliver higher doses of radiation to a local tumor while sparing surrounding tissues, thus minimizing

radiation-induced liver damage. Additionally, a meta-analysis[31] showed that transcatheter arterial yttrium-90 radioembolization (TRAE) facilitated downstaging for potential surgical resection in 11% of unresectable ICC cases. Furthermore, survival rate analysis revealed a combined median overall survival of 12.7 months, demonstrating the potential of these therapies.

In recent years, there has been an exploratory shift towards the combined use of radiotherapy and chemotherapy in treating ICC. Retrospective studies[32,33] have suggested that this combined approach significantly outperforms either radiotherapy or chemotherapy alone in terms of tolerance, side effects, local control rate, progression-free survival (PFS), and OS. A study based on the SEER database[34] showed that the survival benefits of the group receiving combined radiotherapy and chemotherapy were higher than those of the group receiving radiotherapy alone. Furthermore, clinical phase II trial results for 41 cases of locally advanced ICC treated with radioembolization (SIRT) plus chemotherapy demonstrated an objective response rate of 39% at three months, a median progression-free survival of 14 months (95% CI, 8-17 months), and a median overall survival of 22 months (95% CI, 14-52 months). Nine patients (22%) could be downstaged for surgical intervention, and eight patients (20%) ultimately achieved R0 (microscopically negative margins) resection. The study concluded that for unresectable ICC patients, SIRT combined with chemotherapy has an anti-tumor effect, and a significant proportion of patients can be downstaged for surgical intervention[8]. Another phase II study[35] indicated that combined local fluorouracil and high-dose conformal radiotherapy (median dose 60.75 Gy) for inoperable intrahepatic malignant tumors (with ICC accounting for approximately 35.9%, 46/128) resulted in a median survival of 15.8 months. All of these studies highlight the potential value of combining radiotherapy and chemotherapy in the treatment of unresectable ICC.

A population-based cohort study, based on the Cancer Registry database of Taiwan[36], included 844 cases of inoperable, non-metastatic ICC patients. They were divided into four groups: synchronous radiotherapy and chemotherapy, sequential chemoradiotherapy, chemotherapy alone, and palliative symptomatic treatment. The results of multivariate analysis indicated that synchronous radiotherapy and chemotherapy could reduce the risk of death by 35% compared to palliative treatment, and it was superior to sequential chemoradiotherapy and chemotherapy alone. Our study enrolled 11,753 patients with advanced unresectable ICC, and reported similar findings. The research discovered that compared to the chemotherapy alone group, patients in the combined

chemotherapy and radiotherapy group had a significantly reduced risk of death (HR, 0.775; 95% CI, 0.718-0.837, p<0.001). The radiotherapy alone group did not significantly increase the risk of death (HR, 1.070; 95% CI, 0.963-1.188, p=0.207), while the groups that did not receive chemotherapy or radiotherapy showed a significantly increased risk of death (HR, 1.824; 95% CI, 1.744–1.908, p < 0.001). Therefore, combined chemotherapy and radiotherapy can improve the survival benefits for unresectable ICC patients.

In this study, Tables 2 and 3 demonstrate that the differences in overall survival and cancer-specific survival between unresectable ICC patients during 2000-2009 and 2010-2018 were not statistically significant. This finding is based on a multivariate analysis that included patients undergoing various treatment modalities, such as chemotherapy alone (CT), radiotherapy alone (RT), chemoradiotherapy (CT+RT), and no chemotherapy or radiotherapy (NCT+NRT). Previous studies, including ABC-02 and BT22, have demonstrated that gemcitabine combined with cisplatin significantly improves survival outcomes in patients with advanced cholangiocarcinoma compared to gemcitabine monotherapy, establishing it as the standard treatment. While combined chemotherapy (e.g., gemcitabine + cisplatin) during 2010 – 2018 may have provided potential survival benefits compared to monotherapy in 2000 – 2009, other treatment modalities received by patients in this study (e.g., radiotherapy alone, chemoradiotherapy, or no treatment) likely introduced additional complex factors or potential confounders that could have mitigated the survival benefits of combined chemotherapy. This complexity may explain the absence of statistically significant survival differences between the two periods (2000 – 2009 vs. 2010 – 2018) among unresectable ICC patients. Moreover, due to the lack of detailed treatment information in the SEER database (e.g., specific drug types and treatment regimens), this study was unable to further compare the effects of monotherapy and combined chemotherapy on survival rates for unresectable ICC patients across the two time periods. This limitation should be acknowledged, and future research should aim to incorporate more granular treatment data to better evaluate the specific impacts of different treatment regimens on survival outcomes.

Our study cohort, comparable to the SEER database results, included 27 patients who received standalone chemotherapy (average age 58.59 ± 10.02, tumor size 7.77 ± 3.29 cm) and 9 patients who underwent chemotherapy combined with radiation therapy (average age 58.0 ± 5.66, tumor size 6.36 ± 2.66 cm). The median survival times were 9 (range 2-24) months and 11 (range 5-20)

months, respectively (see Supplementary Table 1). While the combined treatment cohort demonstrated a trend toward extended survival, the difference was not statistically significant (P=0.232). This discrepancy might be attributed to the small sample size of this study, indicating a need for further investigation with larger sample sizes.

The main new contributions of this study include: First, based on large-scale data from the SEER database, we analyzed the impact of different treatment strategies (such as monotherapy, chemoradiotherapy, radiotherapy, and no treatment) on the survival rate of unresectable ICC patients, providing important insights for personalized treatment. Second, this is the largest comparative study to date on treatment strategies for unresectable ICC patients, ensuring the broad applicability and high statistical power of the results. Finally, the study highlights the limitations of the data, particularly the lack of treatment details, and emphasizes the need for future evaluations of treatment regimens through more precise clinical data and multi-center trials.

However, it has its limitations: Firstly. the absence of specific radiation therapy data. The SEER database does not provide details like the dose, fractionation, field size, prescription point/volume, and other parameters of radiation therapy. It also lacks information on brachytherapy, including particle type, activity, prescription dose, and radiation-related toxicities. These factors could significantly affect treatment decisions and outcomes. Secondly. The unavailability of specific chemotherapy information. The database does not record the types of chemotherapy drugs, combination regimens, and chemotherapy-related toxicities. For instance, the default first-line treatment for advanced biliary tract cancer is gemcitabine combined with cisplatin, a finding based on the ABC-02 study[5] published in NEJM in 2010. Patients diagnosed with ICC before 2010 might have received less effective or outdated chemotherapy regimens, potentially compromising treatment efficacy. Thirdly. The omission of patient-specific factors: Patients' overall health, liver function, and comorbidities, crucial factors affecting survival are not available in the SEER database. Fourthly. The non-randomized nature of the study: The current study's non-randomized design inherently leads to selection bias and the influence of unregistered variables in the database. Fifthly. Potential imbalance between treatment groups: Differences in patient characteristics or other unexplained variables between treatment groups may result in biased outcomes.

In conclusion, our study suggests that patient age, gender, grade classification, tumor diameter, and treatment modality act as independent prognostic factors for unresectable advanced ICC

patients. For these patients, combined chemoradiotherapy significantly improves the overall survival compared to either chemotherapy or radiotherapy alone. However, further confirmation of the role of combined chemoradiotherapy in the treatment of unresectable ICC patients necessitates prospective, large-sample, randomized controlled trials

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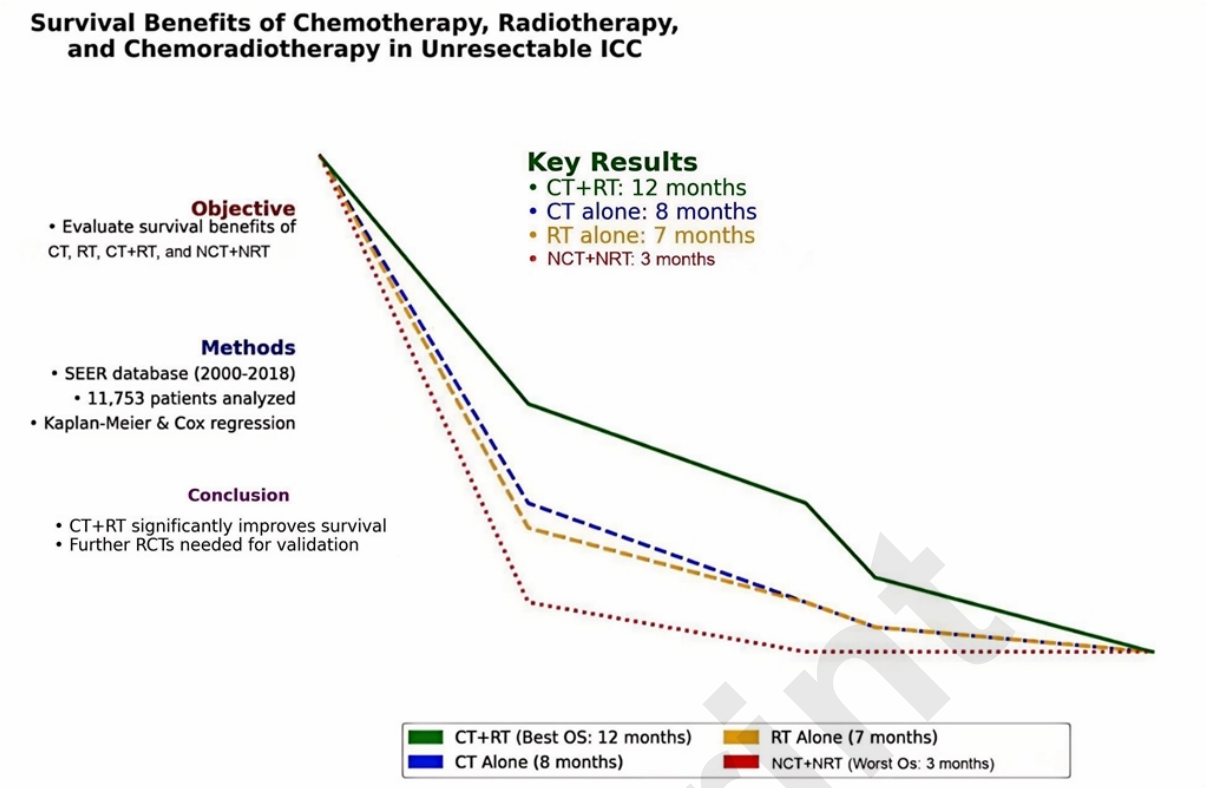

Survival Benefits of Chemotherapy, Radiotherapy, and Chemoradiotherapy in Unresectable ICC
Objective
• Evaluate survival benefits of CT, RT, CT+RT, and NCT+NRT
Methods
• SEER database (2000-2018)
• 11,753 patients analyzed
• Kaplan-Meier & Cox regression
Conclusion
• CT+RT significantly improves survival
• Further RCTs needed for validation
Key Results
• CT+RT: 12 months
• CT alone: 8 months
• RT alone: 7 months
• NCT+NRT: 3 months
CT+RT (Best OS: 12 months)
CT Alone (8 months)
RT Alone (7 months)
NCT+NRT (Worst Os: 3 months)

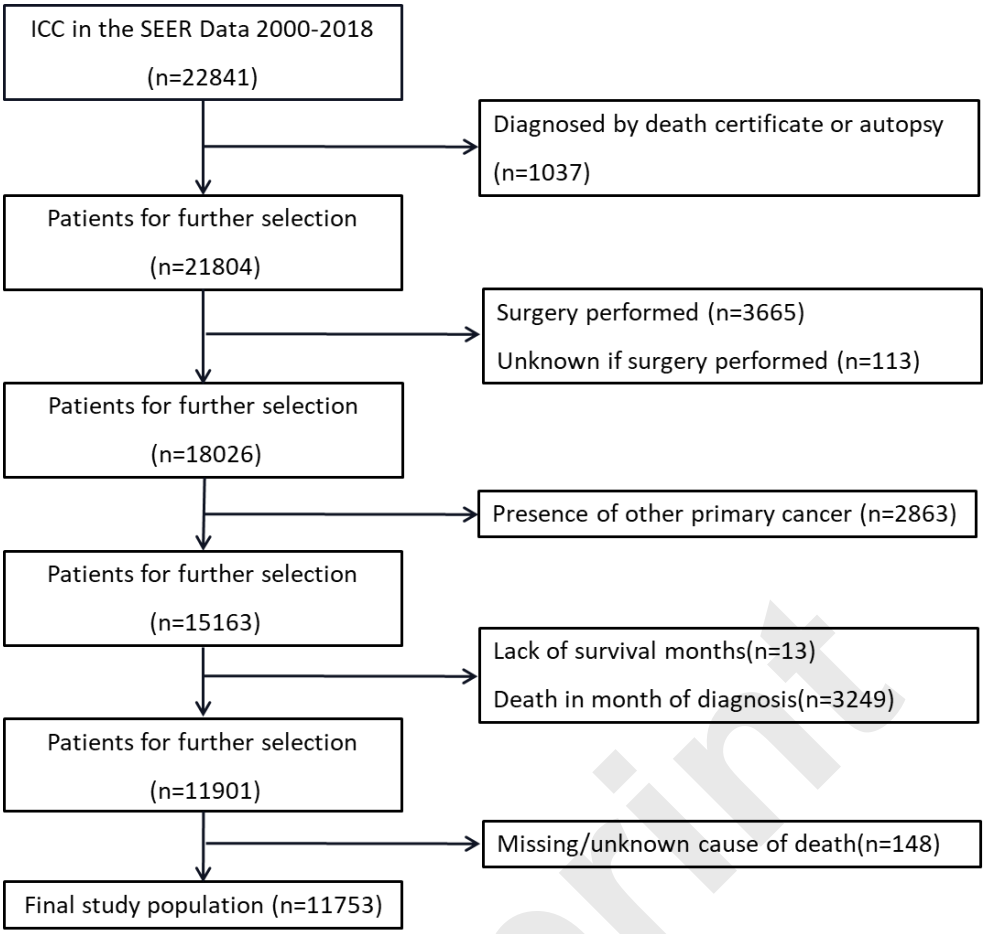


Figure 1 Flowchart for selection of the study population from SEER database. ICC: Intrahepatic Cholangiocarcinoma; SEER: Surveillance, Epidemiology, and End Results.

Table 1 Baseline characteristics according to treatment regimens

Characteristics	Overall (N=11753)	CT Alone (N=4531)	CT+RT (N=996)	NCT+NRT (N=5744)	RT Alone (N=482)	P value
Year.of.diagnosis						<0.001
2000-2009	4678 (39.8%)	1330 (29.4%)	342 (34.3%)	2839 (49.4%)	167 (34.6%)	
2010-2018	7075 (60.2%)	3201 (70.6%)	654 (65.7%)	2905 (50.6%)	315 (65.4%)	
Agegroup						<0.001
<65 years	4610 (39.2%)	2281 (50.3%)	488 (49.0%)	1691 (29.4%)	150 (31.1%)	
≥65 years	7143 (60.8%)	2250 (49.7%)	508 (51.0%)	4053 (70.6%)	332 (68.9%)	
Sex						0.3924
Female	5682 (48.3%)	2165 (47.8%)	482 (48.4%)	2815 (49.0%)	220 (45.6%)	
Male	6071 (51.7%)	2366 (52.2%)	514 (51.6%)	2929 (51.0%)	262 (54.4%)	
Race						0.0003
Black	1096 (9.3%)	390 (8.6%)	66 (6.6%)	590 (10.3%)	50 (10.4%)	
White	9080 (77.3%)	3568 (78.7%)	798 (80.1%)	4343 (75.6%)	371 (77.0%)	
Others	1577 (13.4%)	573 (12.6%)	132 (13.3%)	811 (14.1%)	61 (12.7%)	

Characteristics	Overall (N=11753)	CT Alone (N=4531)	CT+RT (N=996)	NCT+NRT (N=5744)	RT Alone (N=482)	P value
Marital status						<0.001
Married	6378 (54.3%)	2837 (62.6%)	660 (66.3%)	2615 (45.5%)	266 (55.2%)	
Unmarried	4904 (41.7%)	1561 (34.5%)	312 (31.3%)	2837 (49.4%)	194 (40.2%)	
Unknown	471 (4.0%)	133 (2.9%)	24 (2.4%)	292 (5.1%)	22 (4.6%)	
Grade						<0.001
I-II	1622 (13.8%)	712 (15.7%)	161 (16.2%)	672 (11.7%)	77 (16.0%)	
III-IV	1828 (15.6%)	790 (17.4%)	157 (15.8%)	816 (14.2%)	65 (13.5%)	
Unknown	8303 (70.6%)	3029 (66.9%)	678 (68.1%)	4256 (74.1%)	340 (70.5%)	
Sizegroup						<0.001
>5cm	5910 (50.3%)	2310 (51.0%)	447 (44.9%)	2946 (51.3%)	207 (42.9%)	
≤5cm	1236 (10.5%)	425 (9.4%)	152 (15.3%)	583 (10.1%)	76 (15.8%)	
Unknown	4607 (39.2%)	1796 (39.6%)	397 (39.9%)	2215 (38.6%)	199 (41.3%)	
Cause.of.death						<0.001
Alive/dead not from cancer	646 (5.5%)	165 (3.6%)	45 (4.5%)	404 (7.0%)	32 (6.6%)	

Characteristics	Overall (N=11753)	CT Alone (N=4531)	CT+RT (N=996)	NCT+NRT (N=5744)	RT Alone (N=482)	P value
Dead from cancer	11107 (94.5%)	4366 (96.4%)	951 (95.5%)	5340 (93.0%)	450 (93.4%)	

P values computed from Pearson's $\chi 2$ test. CT, chemotherapy; RT, radiotherapy; NCT, non- chemotherapy; NRT, non- radiotherapy.

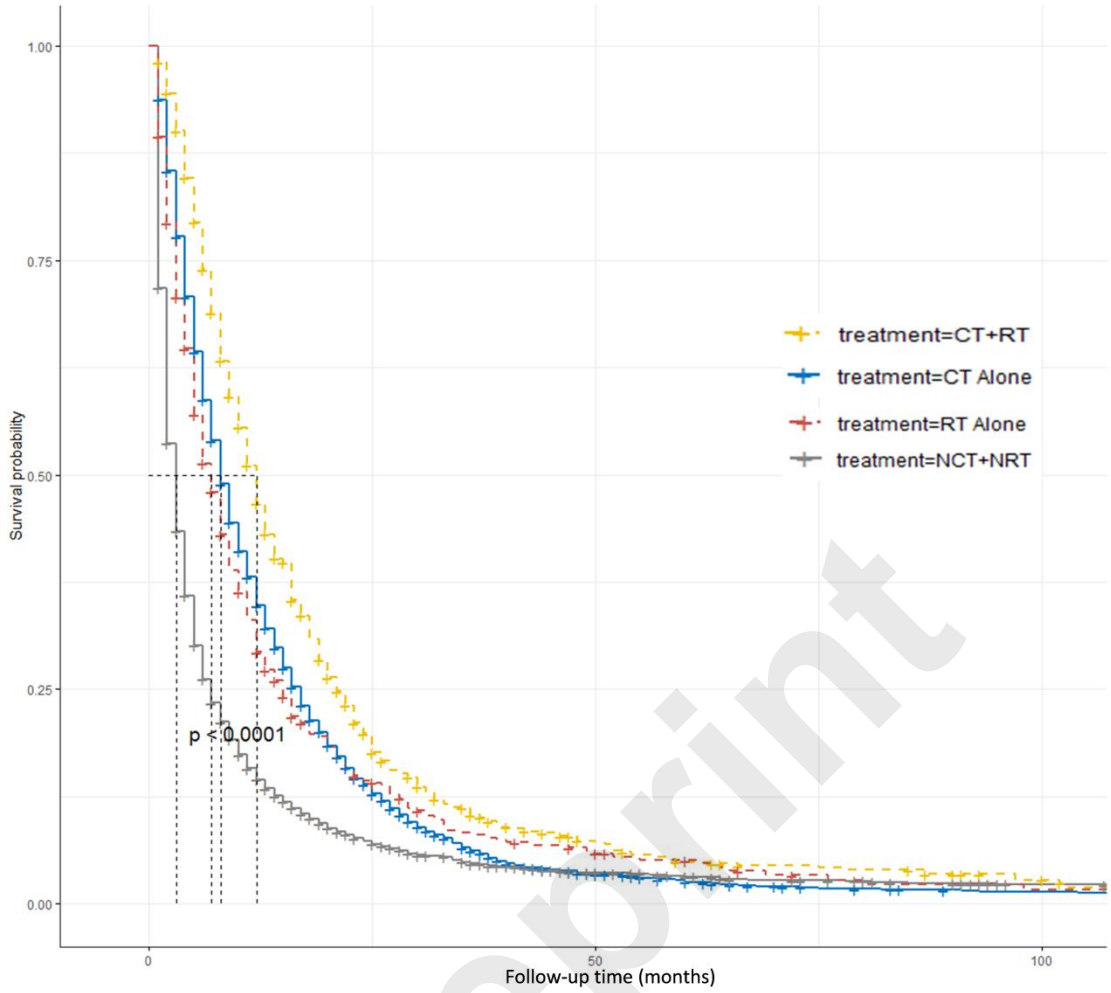


Figure 2 Kaplan–Meier analysis for overall survival of ICC patients according to treatment regimens

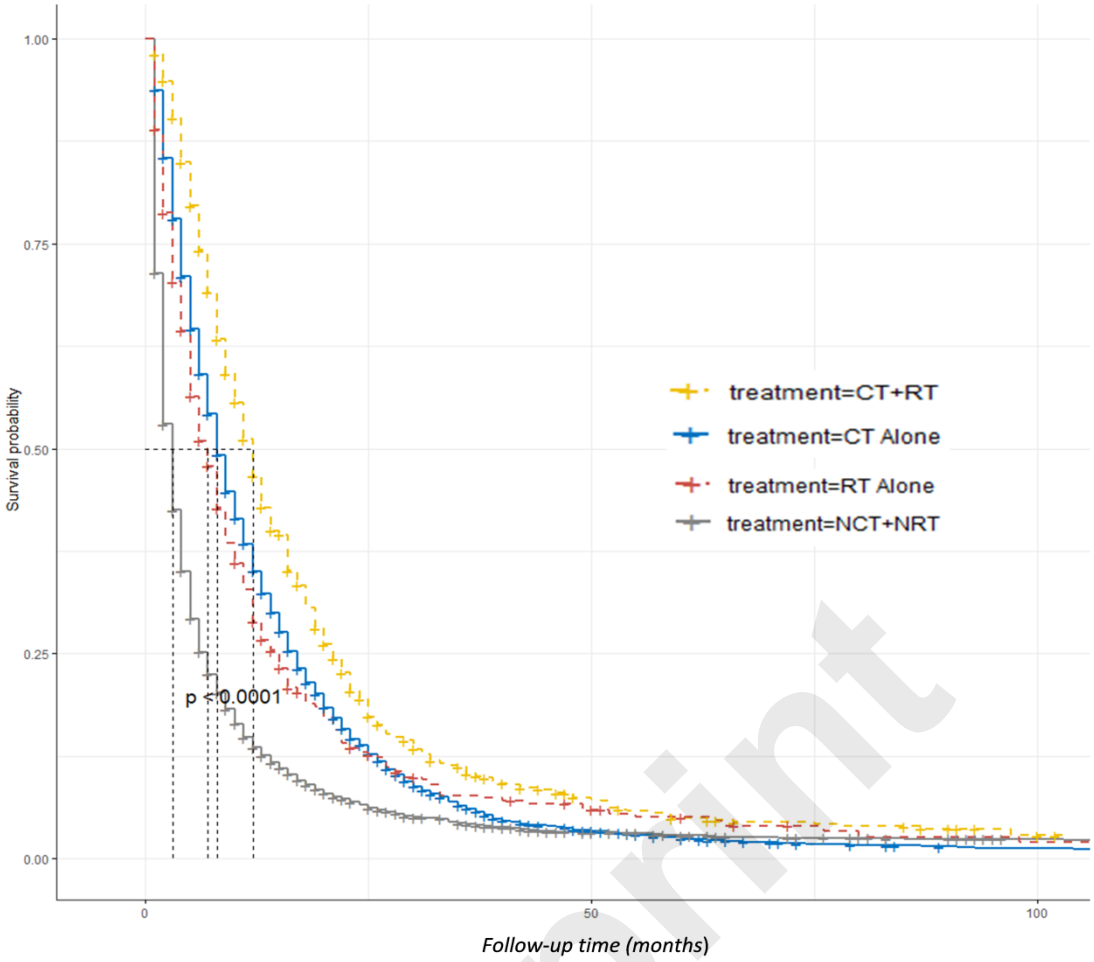


Figure 3 Kaplan–Meier analysis for cancer-specific survival of ICC patients according to treatment regimens.

Table 2 Predictors for overall survival of unresectable ICC patients

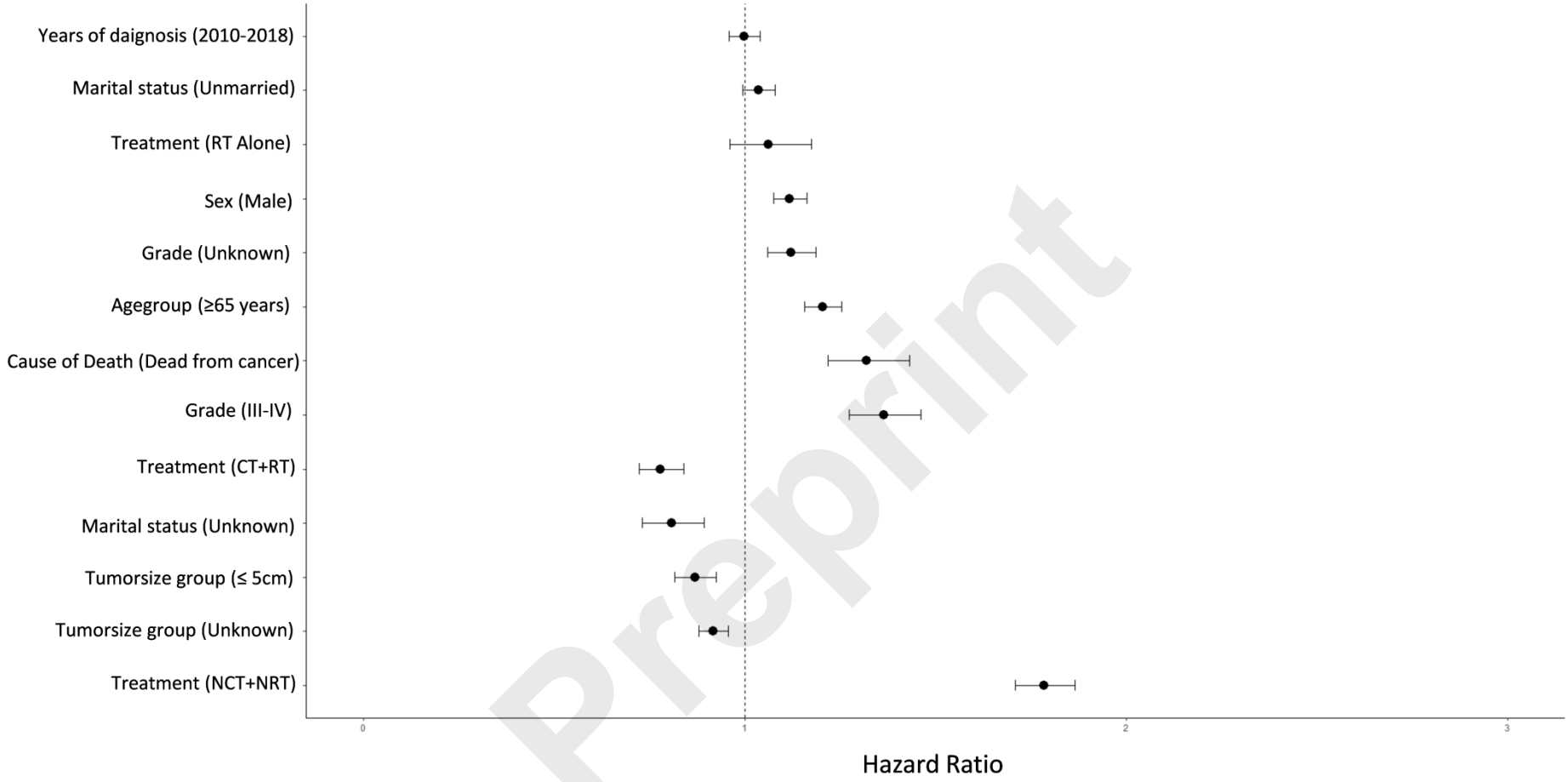
Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Year.of.diagnosis				
2000-2009	Reference		Reference	
2010-2018	0.870 (0.837-0.904)	<0.001	0.998 (0.959-1.039)	0.919
Agegroup				
<65 years	Reference		Reference	
≥65 years	1.296 (1.247-1.348)	<0.001	1.204 (1.157-1.254)	<0.001
Sex				
Female	Reference		Reference	
Male	1.098 (1.057-1.141)	<0.001	1.117 (1.075-1.162)	<0.001
Race				
Black	Reference			
White	0.960 (0.899-1.025)	0.223		
Others	0.930 (0.857-1.009)	0.081		
Marital status				
Married	Reference		Reference	
Unmarried	1.115 (1.072-1.159)	<0.001	1.035 (0.994-1.078)	0.093
Unknown	0.928 (0.841-1.026)	<0.001	0.808 (0.730-0.893)	<0.001
Grade				
I-II	Reference		Reference	
III-IV	1.356 (1.265-1.453)	<0.001	1.364 (1.273-1.462)	<0.001
Unknown	1.213 (1.147-1.282)	<0.001	1.121 (1.060-1.185)	<0.001
Sizegroup				
>5cm	Reference		Reference	
≤5cm	0.869 (0.817-0.925)	<0.001	0.869 (0.816-0.925)	<0.001
Unknown	0.940 (0.902-0.980)	<0.001	0.917 (0.880-0.956)	<0.001
Treatment				
CT Alone	Reference		Reference	
CT+RT	0.774 (0.718-0.834)	<0.001	0.779 (0.723-0.840)	<0.001
RT Alone	1.068 (0.967-1.181)	0.193	1.061 (0.960-1.174)	0.247
NCT+NRT	1.792 (1.719-1.868)	<0.001	1.785 (1.708-1.865)	<0.001
Cause.of.death				
Alive/dead not from cancer	Reference		Reference	
Dead from cancer	1.116 (1.030-1.209)	<0.001	1.320 (1.217-1.431)	<0.001

CT, chemotherapy; HR, hazard ratio; ICC: Intrahepatic Cholangiocarcinoma; RT, radiotherapy; NCT, non-chemotherapy; NRT, non- radiotherapy.

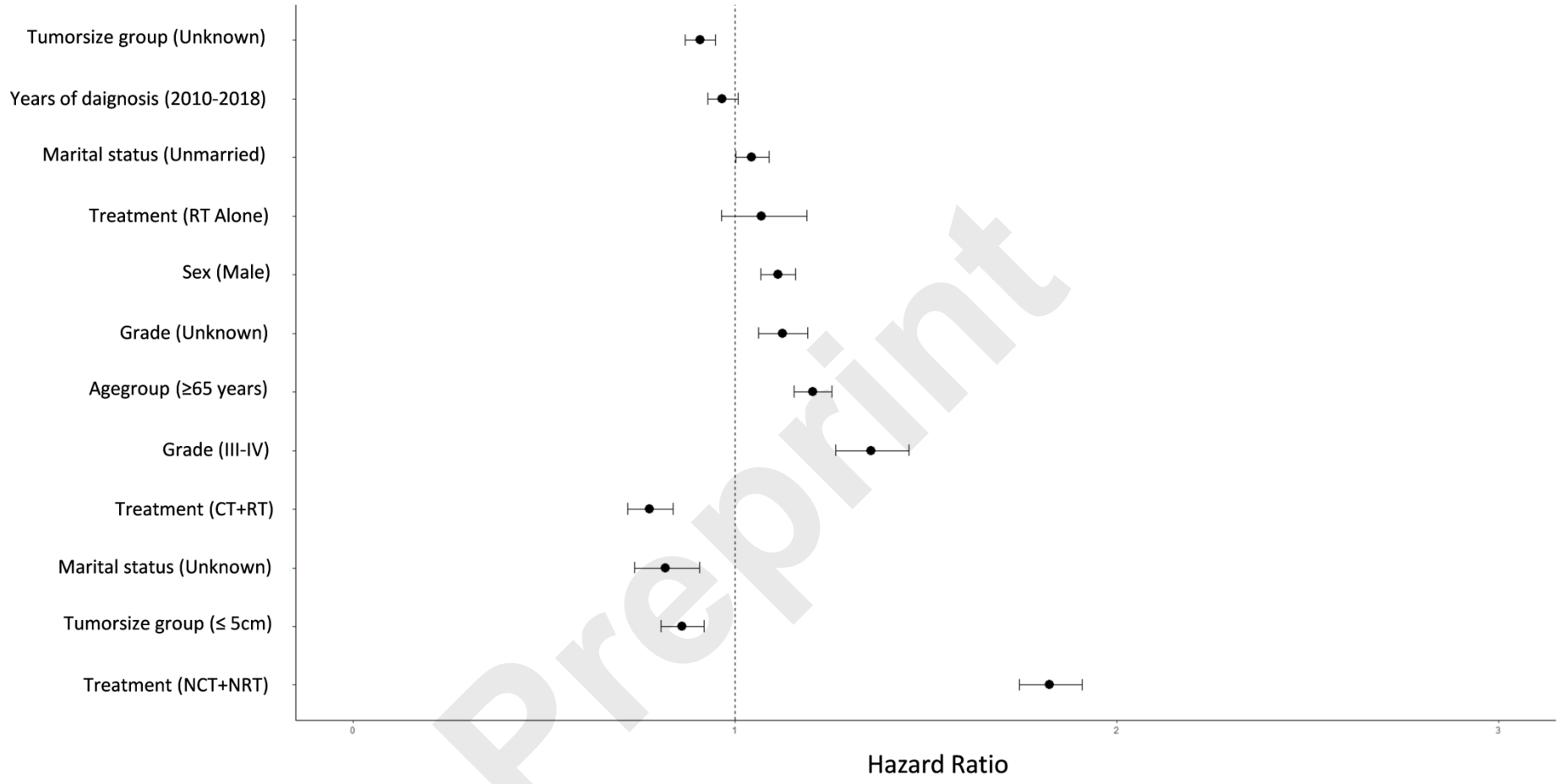
Table 3 Predictors for cancer-specific survival of unresectable ICC patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Year.of.diagnosis				
2000-2009	Reference		Reference	
2010-2018	0.834 (0.801-0.867)	<0.001	0.967 (0.928-1.008)	0.110
Agegroup				
<65 years	Reference		Reference	
≥65 years	1.309 (1.257-1.363)	<0.001	1.203 (1.154-1.254)	<0.001
Sex				
Female	Reference		Reference	
Male	1.097 (1.055-1.141)	<0.001	1.112 (1.068-1.158)	<0.001
Race				
Black	Reference			
White	0.967 (0.903-1.036)	0.339		
Others	0.932 (0.857-1.015)	0.105		
Marital status				
Married	Reference		Reference	
Unmarried	1.137 (1.092-1.184)	<0.001	1.044 (1.001-1.089)	0.044
Unknown	0.945 (0.853-1.048)	0.285	0.818 (0.737-0.907)	<0.001
Grade				
I-II	Reference		Reference	
III-IV	1.344 (1.252-1.443)	<0.001	1.356 (1.263-1.456)	<0.001
Unknown	1.219 (1.151-1.291)	<0.001	1.124 (1.061-1.191)	<0.001
Sizegroup				
>5cm	Reference		Reference	
≤5cm	0.856 (0.802-0.914)	<0.001	0.861 (0.807-0.919)	<0.001
Unknown	0.929 (0.890-0.970)	<0.001	0.908 (0.870-0.948)	<0.001
Treatment				
CT Alone	Reference		Reference	
CT+RT	0.773 (0.716-0.835)	<0.001	0.775 (0.718-0.837)	<0.001
RT Alone	1.090 (0.982-1.209)	0.105	1.070 (0.963-1.188)	0.207
NCT+NRT	1.880 (1.801-1.961)	<0.001	1.824 (1.744-1.908)	<0.001

CT, chemotherapy; HR, hazard ratio; ICC: Intrahepatic Cholangiocarcinoma; RT, radiotherapy; NCT, non-chemotherapy; NRT, non- radiotherapy.



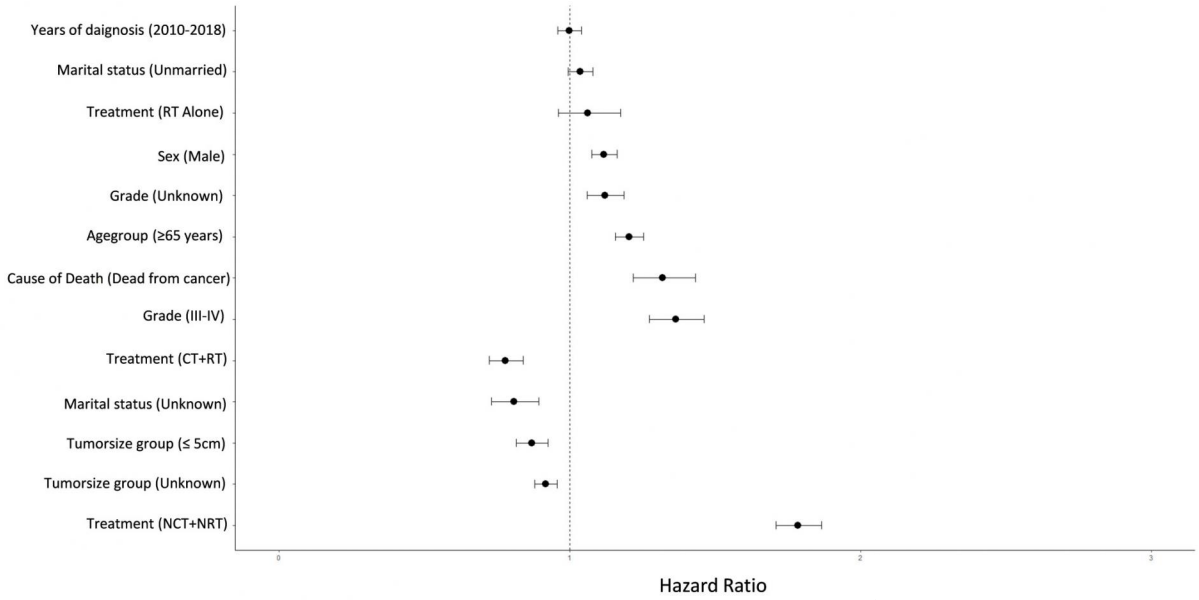
Supplementary Figure 1 Forest plot for overall survival

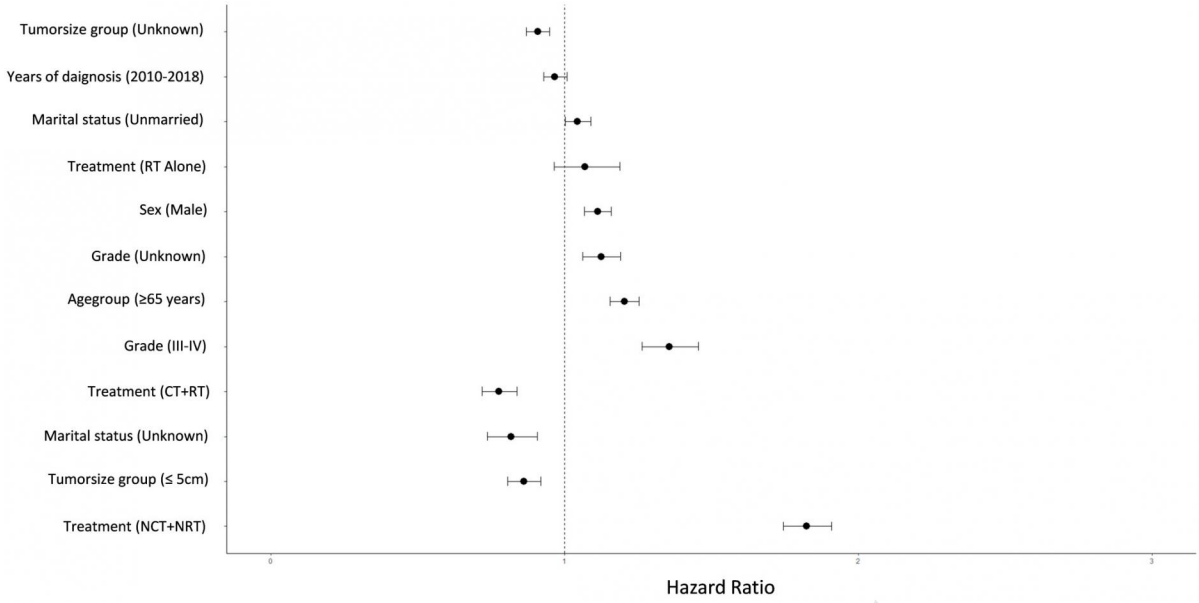


Supplementary Figure 2 Forest plot for cancer-specific survival

Supplementary Table 1 Characteristics of included unresectable ICC patients in our institution

Characteristics	**CT (n=27)**	**CT plus RT (n=9)**	***P***
Age (year)	58.59 ±10.02	58.0 ± 5.66	*0.868*
Sex			*0.555*
Male	15	6	
Female	12	3	
Tumor size(cm)	7.77 ± 3.29	6.36 ± 2.66	*0.252*
Tumor stage			*0.501*
T2	7	1	
T3	5	3	
T4	15	5	
Nodal status			*0.776*
N0	4	1	
N1	23	8	
Metastasis Stasus			*0.169*
M0	9	1	
M1	18	8	
Median survival (month)	9 (2-24)	11 (5-20)	*0.232*


Years of daignosis (2010-2018)
Marital status (Unmarried)
Treatment (RT Alone)
Sex (Male)
Grade (Unknown)
Agegroup (≥65 years)
Cause of Death (Dead from cancer)
Grade (III-IV)
Treatment (CT+RT)
Marital status (Unknown)
Tumorsize group (≤ 5cm)
Tumorsize group (Unknown)
Treatment (NCT+NRT)
0
1
2
3
Hazard Ratio


Tumorsize group (Unknown)
Years of daignosis (2010-2018)
Marital status (Unmarried)
Treatment (RT Alone)
Sex (Male)
Grade (Unknown)
Agegroup (≥65 years)
Grade (III-IV)
Treatment (CT+RT)
Marital status (Unknown)
Tumorsize group (≤ 5cm)
Treatment (NCT+NRT)
0
1
2
3
Hazard Ratio