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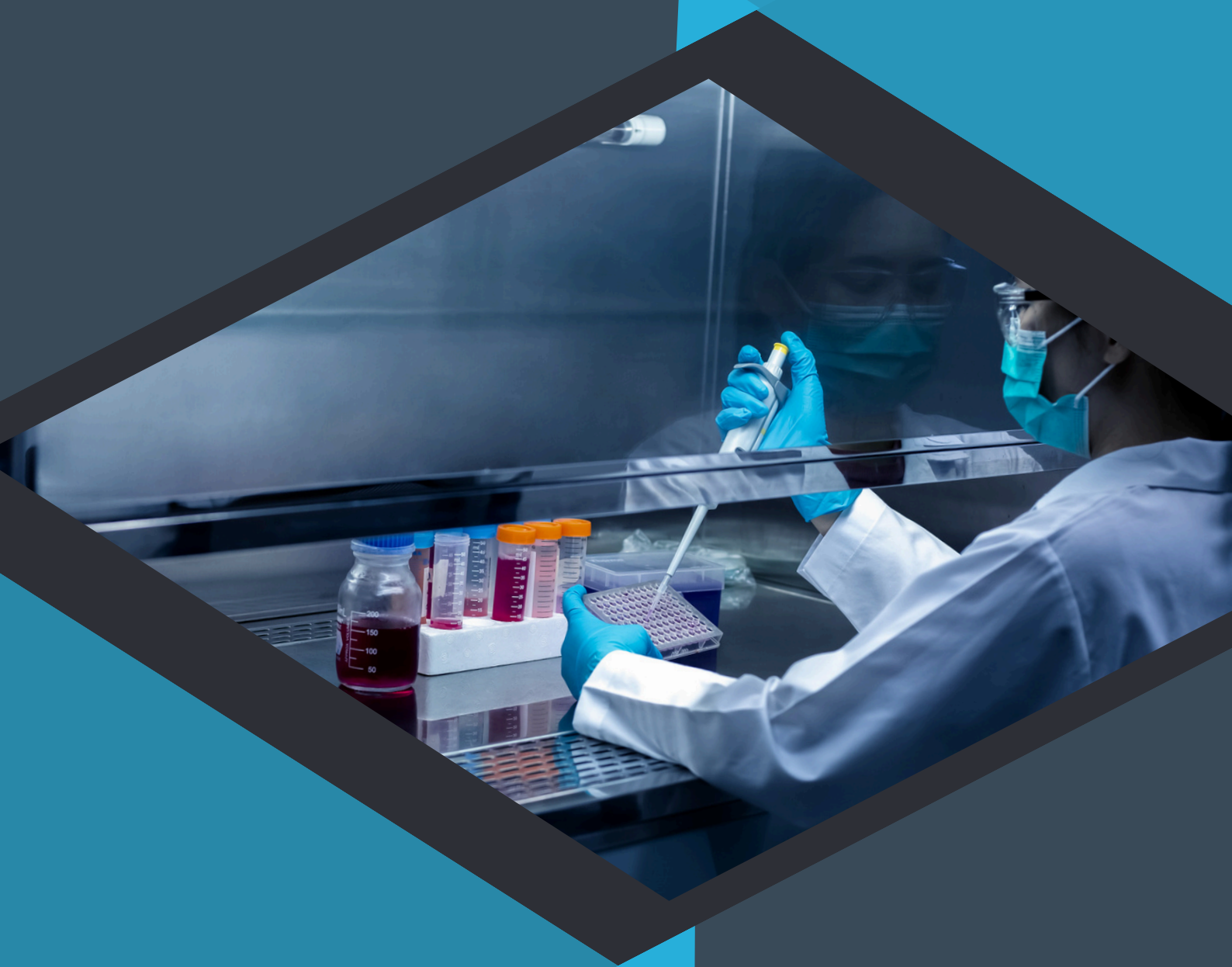

Innovations in cancer diagnostics

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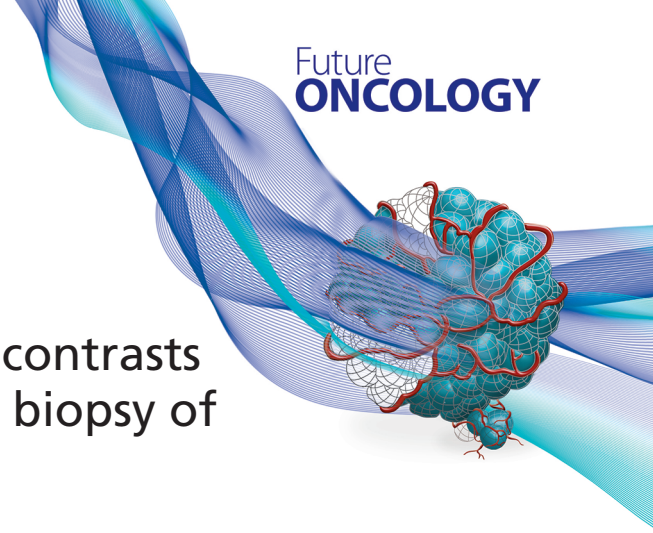

A new fluorescent targeting tracer contrasts dual tracers in sentinel lymph node biopsy of breast cancer

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Purpose: To explore the clinical application value of indocyanine green (ICG)–rituximab in sentinel lymph node biopsy. **Methods:** This study included 156 patients with primary breast cancer: 50 patients were enrolled in dose-climbing test, and 106 patients were enrolled in verification test. This was to compare the consistency of ICG–rituximab and combined method in the detected lymph nodes. **Results:** According to the verification test, the imaging rate of ICG–rituximab was 97.3%. Compared with the combined method, the concordance rate of fluorescence method was 0.991 (28 + 78/107; $p < 0.001$). **Conclusion:** For ICG–rituximab as a fluorescent targeting tracer, the optimal imaging dose of ICG 93.75 μg/rituximab 375 μg can significantly reduce the imaging of secondary lymph nodes. Compared with the combined method, it has a higher concordance rate.

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Keywords: breast cancer • dose-climbing test • fluorescent targeting tracer • ICG • ICG–rituximab • rituximab • sentinel lymph node • SLNB • tracer • verification test

In patients with clinically negative lymph nodes, sentinel lymph node biopsy (SLNB) instead of axillary lymph node dissection (ALND) has no difference in regional control, disease-free and overall survival, and can improve quality of life and upper limb function [1–4]. The combination of patent blue and radioisotope can provide the success rate of sentinel lymph node (SLN) detection [3], but these approaches present specific advantages and drawbacks.

The fluorescent tracer indocyanine green (ICG) has advantages such as economy, safety and visibility [5,6], but ICG is a small molecule tracer, which has the shortcomings of short trace time and high rate of nonsentinel lymph node (n-SLN) imaging. ICG was combined with rituximab directly to produce a new receptor-targeted tracer (ICG–rituximab), which specifically binds to CD20 molecules on the surface of B lymphocytes in the SLN and has SLNB targeting [7]. The aim of this study was to establish the optimal dose and feasibility of ICG–rituximab as a tracer of SLNB in breast cancer, which were tested by combined (methylene blue and a radioisotope) method.

Materials & methods

Patients

The sample size was calculated by the sample size formula ($n = [\mu\alpha/\delta]^2[1\text{-}p]p$). Setting: the false negative rate of SLNB was less than 10% and the positive rate of SLNs was 30%. μα: 1.960; δ: 0.1; p: 0.9; n: 105.

This study included 156 patients with primary breast cancer in the Breast Disease Center of Shandong Cancer Hospital from January 2016 to September 2019: 50 patients were enrolled in the ICG–rituximab dose-climbing test and 106 patients were enrolled in the ICG–rituximab verification test. The protocol and consent forms were approved by the Institutional Ethics Committee (No. SDTHEC20110324).

The enrollment criteria included clinical physical examination and ultrasonography of primary breast cancer patients with negative axillary lymph nodes, and no distant metastasis was found in imaging examination. The

Table 1. Instruments and reagents.

	Specifications/models	Provider
Radioisotope	^{99m}Tc-labeled sulfur colloid	Beijing New Kostar company, prepared by nuclear medicine department of Shandong Cancer Hospital (Beijing, China)
Dye	Methylene blue 20 mg 2 ml	Jichuan Pharmaceutical Group Co., Ltd (Jiangsu, China)
Indocyanine green	25 mg	Dandong Yichuang Pharma, Ltd (Dandong, China)
Rituximab	100 mg	Shanghai Roche Pharmaceuticals (Shanghai, China)
Near-infrared fluorescence imaging system	MI-1 fluorescence imaging system	Mingde Biotech, Ltd (Hebei, China)
Gamma probe detection	Neoprobe, Neo2000 gamma detection system	Johnson and Johnson (Shanghai, China)

exclusion criteria included breast cancer patients who had received neoadjuvant therapy, had previous axillary surgery history and had inflammatory breast cancer.

Indocyanine green–rituximab dose-climbing test

The coupling mass ratio of ICG to rituximab is 1:4 [8], and the 0.05 ml of rituximab solution (10 mg/ml) and ICG solution (2.5 mg/ml) were extracted and mixed with a 1 ml syringe, and diluted with sterilized water for injection to 1.0 ml (125 μg/500 μg) as mother solution. A total of 100, 75, 50, 20 and 10% of the mother liquor were extracted and diluted to 1.0 ml with sterilized injection water as five groups of reagents. The mass ratio of each group of reagents was as follows: group A 625 μg (125 μg/500 μg); group B 468.75 μg (93.75 μg/375 μg); group C 312.5 μg (62.5 μg/250 μg); group D 125 μg (25 μg/100 μg) and group E 62.5 μg (12.5 μg/50 μg).

Indocyanine green–rituximab verification test

Rituximab solution (10 mg/ml) 0.1 ml and ICG solution (2.5 mg/ml) 0.1 ml were extracted with a 1 ml syringe, then mixed and diluted to 0.8 ml with sterilized water for injection. A total of 0.3 ml was taken as the injection dose, and the mass was 468.75 μg (93.75 μg/375 μg).

Instruments & reagents

The test instruments and reagents are shown in Table 1.

Axillary sentinel lymph node biopsy

Indocyanine green–rituximab dose-climbing test

From 3 to 18 h before operation, different doses of ICG–rituximab were injected into the glandular layer of the affected breast (group A 625 μg; group B: 468.75 μg; group C: 312.5 μg; group D: 125 μg; group E: 62.5 μg). The volume of the injection reagent was 1 ml.

Indocyanine green–rituximab verification test

In each patient, ^{99m}Tc-SC (1.0–1.2 ml/22.2–55.5 MBq) was injected into the mammary gland at 6 and 12 o'clock of the areola surrounding area with the guidance of ultrasound and ICG–rituximab 0.3 ml (ICG 93.75 μg/rituximab 375 μg) was injected intradermally near the areola in the upper outer quadrant 3–18 h before surgery. After general anesthesia, near-infrared fluorescence imaging system was used to label the luminous lymphatic vessels and lymph nodes percutaneously, and gamma detection probe was used to label the 'hot spots' of lymph nodes. SLNB was performed 10–15 min after subcutaneous injection of 1% methylene blue 4 ml on the surface of primary tumor. Gamma detection probe identified all nodes with count rates greater than 10% of the nodes with the highest count rate, that is, hot nodes. Blue dye nodes and hot nodes were defined as SLNs. Palpation of the axilla was performed, and palpated enlarged hard lymph nodes were removed and recorded as palpation SLNs. The SLNs were detected by near-infrared fluorescence imaging system, and the gray values of SLNs were recorded by ICG–rituximab imaging.

Mode of operation

SLNB has become the standard procedure of breast cancer surgery, so it is difficult to verify the diagnostic efficiency of ICG–rituximab by ALND. We cannot compare ALND to obtain an accurate false negative rate. Patients who agree to replace ALND with SLNB are not allowed to undergo ALND if there is no metastasis in SLN diagnosed

Table 2. Characteristics of indocyanine green–rituximab dose-climbing test cases (n = 50).

Characteristic	A	B	C	D	E	p-value
n	10	10	10	10	10	
Age						0.757
<40 years	2	1	2	3	1	
From 40 to approximately 59 years	7	7	6	6	5	
>59 years	1	2	2	1	4	
Tumor size (cm)	2.283	2.018	2.267	2.152	2.087	0.341
Tumor site						0.872
Upper outer quadrant	5	6	5	5	4	
Lower outer quadrant	1	2	1	1	1	
Upper inner quadrant	2	1	2	1	0	
Lower inner quadrant	1	1	1	1	4	
Central	1	1	1	2	1	
Histological grading						0.315
Carcinoma *in situ*	4	1	1	3	1	
I	0	0	0	0	1	
II	3	6	7	7	7	
III	3	3	2	0	1	

by frozen pathology and print cytology. Patients without metastasis of SLNs only underwent SLNB. Patients with intraoperative or postoperative diagnosis of SLN metastases undergo ALND.

Pathologic evaluation

All SLNs were examined by intraoperative frozen section and printed cytology and postoperative routine paraffin pathological examination. According to the 8th edition of American Joint Committee on Cancer, macrometastases, micrometastases and isolated tumor cells are defined as SLN positive.

Drug safety

The allergic reaction symptoms such as skin swelling, papule, palpitation and respiratory allergy were observed after ICG–rituximab was injected into the breast. The eosinophils were measured on the first day after operation.

Statistical analysis

SPSS 22.0 was used for statistical analysis to compare the agreement of ICG–rituximab and combined method in the detection of lymph nodes in SLNB. t-test, chi-square test or Fisher exact probability method were used to analyze the difference of mean between continuous variables and agreement rate. The difference was statistically significant when $\alpha = 0.05$ ($p < 0.05$).

Results

General information & security results

The general data of 156 patients in this study – classification of tumor size, location of tumor, pathological type, mode of operation, BMI, etc. – are shown in Tables 2 & 3. There was no allergic reaction after injection of ICG–rituximab, and the eosinophil count did not increase after operation.

Imaging results of indocyanine green–rituximab dose-climbing test

In the ICG–rituximab dose-climbing test, the imaging rate of all the five groups was 100%, and the imaging rate of SLN tracer was compared as shown in Figure 1. The fluorescence imaging rate of n-SLNs in five groups was 54.1, 6.7, 3, 0 and 0%.

Imaging results of indocyanine green–rituximab verification test

SLNB was performed in 110 cases of breast cancer by fluorescence, nuclide and dye methods, including 107 cases of ICG–rituximab imaging, 108 cases of nuclide imaging, 101 cases of dye imaging and 110 cases of combined

Table 3. Characteristics of indocyanine green–rituximab verification test cases (n = 110).

Characteristic	n (%)
Pathology:	
Noninvasive carcinoma	16 (14.5)
Ductal	86 (78.2)
Lobular	1 (0.9)
Others	7 (6.3)
Tumor site:	
Upper outer quadrant	69 (62.7)
Lower outer quadrant	13 (11.8)
Upper inner quadrant	19 (17.3)
Lower inner quadrant	5 (4.5)
Central	4 (3.6)
BMI:	
BMI<18.5	3 (2.7)
18.5≤BMI<25	70 (63.6)
25≤BMI<30	29 (26.4)
30≤BMI	8 (7.3)
Mode of operation:	
Mastectomy	65 (59.1)
Breast conserving surgery	41 (37.3)
Prosthesis implantation	4 (3.6)
Tumor staging:	
Ductal carcinoma *in situ*	16 (14.5)
T1	63 (57.3)
T2	29 (26.4)
T3	2 (1.8)

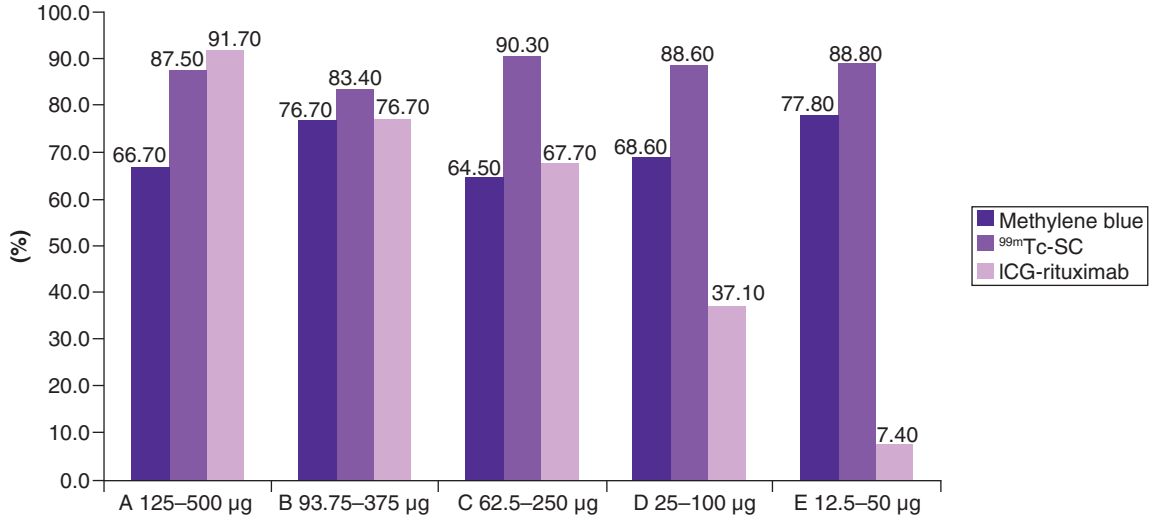

Figure 1. The development of five groups at different doses.
ICG-Rit: Indocyanine green–rituximab.

imaging. SLN metastasis was found in two of three patients whose ICG–rituximab imaging failed. A total of 270 lymph nodes were detected by ICG–rituximab, with the highest gray value of 254, most of which were concentrated in the range from 254 to 220. Those less than 220 were not easily found during the operation, and the gray values were not continuous. The lymph nodes with different gray values are shown in Figure 2.

Agreement evaluation of comparative combined method

Lymph node metastases were detected in 31 SLNs detected by SLNB, of which 30 were detected by the nuclide method, 27 were detected by the dye method, 28 were detected by ICG–rituximab and two failed imaging. According to Table 4, compared with the combined method, the agreement rate of fluorescence method was 0.991 ($28 + 78/107$; $p < 0.001$).

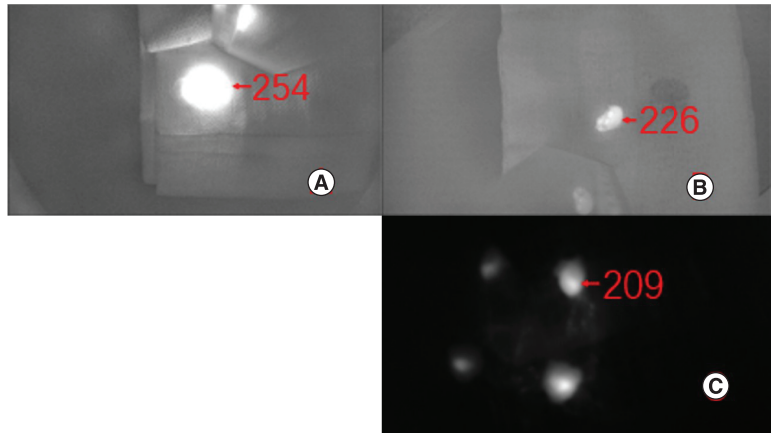

Figure 2. Different gray values of lymph nodes in ICG-Rit imaging. The gray values were 254 **(A)**, 226 **(B)** and 209 **(C)**.
ICG-Rit: Indocyanine green–rituximab.

Table 4. Detection rate of sentinel lymph node by indocyanine green–rituximab and combined method.

Number	Combined +	Combined -	Total ICG	p-value
ICG+	28	0	28	≤ 0.001
ICG-	1	78	79	
Total combined	29	78	107	

Combined tracer: methylene blue and ^{99m}Tc-SC.
ICG: Indocyanine green.

Discussion

In recent years, scholars at home and abroad have tried to study new tracers for SLNB, including ultrasound contrast agents, superparamagnetic iron oxide and fluorescent tracer. ICG, the most commonly used reagent in clinic, can observe the subcutaneous lymphatic drainage pathway and SLN position through the fluorescence imager [5,6], which is economical and visual, and has a high detection rate (93.1–100.0%) [9]. However, ICG imaging time is short (5–15 min), there are more secondary lymph nodes appear in imaging, and the number of lymph nodes detected is more than that of radionuclide or blue dye method [10], which may increase the risk of postoperative upper limb complications and lack of standardized procedures such as optimal concentration, dose and injection time, which hinders its clinical promotion.

Rituximab is a specific humanized monoclonal antibody, which can specifically bind to CD20 molecules on the membrane of B lymphocytes in lymph nodes, and is not easy to dissociate. The chemical structure contains a domain that binds to small molecules and can couple with ICG [11,12]. When ICG and rituximab were coupled at a mass ratio of 1:4, the labeling rate reached 100%, while the integrity and immune activity of the antibody molecules were maintained, and there was no sterility, no pyrogen and no acute toxicity [7,8]. ICG–rituximab has the advantages of uniform molecular weight, close binding to lymph nodes and controllable secondary lymph node imaging.

ICG and rituximab are physically coupled and maintain their original drug characteristics. ICG has been used as a fluorescent agent in clinic for 50 years. It has good safety [13] and has been approved by the US FDA. The main adverse reactions of rituximab are neutropenia and rash (≥10%). The therapeutic dose of rituximab for lymphoma is 630 mg (60 kg, 170 cm). The dose of ICG for choroidal angiography is 25 mg; however, the maximum dosage in this study is ICG 125 μg and rituximab 500 μg, ICG is 0.5% of the above dose, and rituximab is 0.79% of the therapeutic dose. In the trial, ICG–rituximab is used in 156 patients, no allergic reaction is found, and the eosinophil count do not increase after operation. Its security is verified.

In the ICG–rituximab dose-climbing test group, according to the dose decreasing order, the SLN imaging rates of the five groups of ICG–rituximab were 91.7, 76.7, 67.7, 37.1 and 7.4% ($p < 0.05$). Compared with the combined method (nuclides + dyes), group A is slightly higher than the combined method ($p < 0.05$); group B is similar to the combined method ($p = 0.485$); and the three groups C, D and E are lower than the combined method ($p < 0.05$). ALND was performed on patients with SLN metastasis in five groups, and fluorescence imaging of n-SLN was detected. The fluorescence imaging rate of n-SLNs in five groups was 54.1, 6.7, 3, 0 and 0%. In group

A, the imaging rate of SLN was 91.7%, and the imaging rate of n-SLN was 54.1%, indicating that it had labeled too many secondary lymph nodes. In group B, the imaging rate of SLN was 76.7%, and that of n-SLN was 6.7%. The above results show that there is no statistical difference in imaging rate between group B and the combined method, and the imaging rate for n-SLN is low (6.7%). This group of doses (93.75 μg/375 μg) can be used as the optimal imaging dose.

In the ICG–rituximab verification test, the detection rates of ICG–rituximab, nuclide, dye and combined methods were 97.3, 98.2, 91.8 and 100%, respectively. The mean SLN of ICG–rituximab imaging was 2.44 and the median was 2, which was significantly lower than that of SLN detected by radionuclide method (2.83 and 3; $p < 0.001$). A total of 1736 patients were included in 12 studies to compare the SLNB diagnostic efficacy of ICG and nuclide method. The SLN detection mean of ICG was 1.5–3.4, and that of nuclide method was 1.35–2.3. The number of lymph nodes detected by ICG was more than that of nuclide method, but there was no statistical difference between them [14]. From the above results, it is inferred that using ICG–rituximab as a SLNB tracer, the number of lymph node visible in imaging is lower than that of ICG imaging, which reduces the imaging of secondary lymph nodes, which may reduce the risk of postoperative axillary complications.

SLN metastasis was detected in 31 patients by frozen pathology, printed cytology and paraffin pathology, of which 30 cases were detected by radionuclide method, 27 cases by dye method, 31 cases by combined method and 28 cases by ICG–rituximab imaging. Compared with the combined method, the agreement rate of the fluorescence method was 0.991 ($28 + 78/107$; $p < 0.001$). It was inferred from the agreement rate of the fluorescence method that this was in excellent agreement with the combined method.

Previous ICG studies showed that the factors of ICG failure included obesity (BMI ≥30) and SLN macrometastasis. A recent study comparing nuclide tracers showed that the ICG imaging rate was 81.9% and the false negative rate was 34.7%. The patients with overweight (BMI >25) or SLN macrometastases (>2 mm) were related to the low detection rate of ICG ($p = 0.02$) [15]. In this study, ICG–rituximab imaging failed in three cases, and the failed cases were overweight patients. In one of the three patients, three SLNs were detected by nuclide method, and the SLN with the lowest radionuclide count was pathologically macrometastatic lymph nodes, which was similar to previous studies. However, among the patients in this study, the effect of BMI on the number of SLNs detected by fluorescence method was not statistically significant ($p = 0.995$). In the study of Mazouni *et al.*, 46% of the cases were overweight (BMI >25) [15]; according to Table 3, 29 cases (26.4%) were overweight and eight cases (7.3%) were obese in our study. If the number of overweight cases is expanded, the imaging rate may decrease and the failure rate may increase.

Limitations

Our research is single-center, and the sample size is not very sufficient. The ICG–rituximab is a new tracer developed by our team. At present, it is only used in our hospital. Although the number of patients participating in the trial reaches the estimated sample size, there is still data bias, and more patients are needed to reduce the bias and obtain more accurate results. In our center, SLNB has completely replaced ALND for patients with intraoperative and postoperative pathological N0. It is impossible to verify the diagnostic efficacy of fluorescent tracers through ALND of each patient. Taking the combined tracers recommended in the current guidelines as the standard for noninferiority comparison to indirectly test the diagnostic efficacy of fluorescent tracers makes the final results biased. In the follow-up trial, the fluorescence tracer tracing after ALND should be recorded to further verify its diagnostic energy efficiency, but the process of enrolling patients would then become slow. The technical bottleneck of fluorescent tracer is its weak penetration, and the photoacoustic imaging technology with high contrast resolutions and deep imaging depth may help the fluorescent tracer to break through this bottleneck and expand its penetration range [16]. With this technique, ICG–rituximab will not need to look for SLNs along the lymphatic vessels of subcutaneous imaging, but can directly explore the lymph nodes of axillary imaging and detect SLNB. The fluorescent tracer lacks the threshold value as radionuclides (the nuclide count is more than 10% of the maximum nuclide count) to judge whether the imaging lymph node is a SLN. In this study, we tried to use the gray value of lymph node imaging to evaluate the degree of ICG–rituximab labeling lymph nodes, but the gray value of detected lymph nodes was not continuous, concentrated in 254–220, and the gray threshold could not be established to distinguish SLN from n-SLN.

Conclusion

In this study, the optimal imaging dose of ICG–rituximab was detected. Compared with ICG, it can reduce the imaging of secondary lymph nodes. Compared with the combined method, it has higher accuracy, specificity and coincidence rate, and lower false negative rate. As a SLNB tracer, ICG–rituximab has good safety and clinical application value.

Summary points

- Neoadjuvant therapy has become the standard treatment for patients with inoperable as well as some invasive and high-risk breast cancers.
- Indocyanine green (ICG)–rituximab was used to set up five groups of dose-increasing test to compare the success rate of development and to select the optimal dose.
- Sentinel lymph node biopsy was performed by using the optimal dose of ICG–rituximab and the combined method to test the agreement between them.
- ICG–rituximab has good safety.
- There may be a decrease in the success rate of ICG–rituximab in obese women, which needs to be confirmed by further trial results.
- Axillary lymph node dissection cannot be performed in the test, and there is a lack of data such as the false negative rate of ICG–rituximab.
- The fluorescence penetration of ICG is weak. It can be combined with photoacoustic imaging technology to optimize fluorescence imaging and improve the detection rate and success rate.
- Photoacoustic imaging technology will be introduced in the next test to detect the imaging results of ICG rituximab in breast sentinel lymph node biopsy again.

Author contributions

QS Zhang, PP Li and S Wu were responsible for study conception and design. X Sun, BB Cong and YS Wang were responsible for acquisition of data and analysis. S Wu, PP Li and YS Wang were responsible for drafting of the manuscript. All authors were responsible for interpretation of data/results and revision of the manuscript.

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Competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

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•• **A new technology can further improve the diagnostic performance of indocyanine green.**

Could imaging after just 1 week predict advanced melanoma treatment response?

A recent study has uncovered that imaging the tumors of patients with advanced melanoma receiving Keytruda® (pembrolizumab) after only 1 week, rather than the standard of approximately 3 months, identified metabolic changes that corresponded with treatment response and progression-free survival (PFS). In this interview, Senior Editor Jade Parker, speaks with the lead author of the study Michael Farwell (University of Pennsylvania, PA, USA) about how imaging at 1 week could improve treatment outcomes and the next steps for this innovative trial.

The study focused on imaging patients after just 1 week of initiating pembrolizumab, compared to traditional 3-month monitoring. What led you to explore this early time point?

Our neoadjuvant trial showed that patients were having complete pathologic responses to immunotherapy by 3 weeks, meaning that the tumor was completely gone. This was a surprising result, which told me that if we wanted to capture the peak immune response, when tumors were infiltrated by activated immune cells but not yet completely cleared by the immune system – then we would need to look earlier. That is why we focused on imaging at 1 week in this trial, with the hope that we might capture the peak immune response at that time. But we didn't know what we were going to find. So, we were really excited when we saw that there were dramatic changes in 18F-fluorodeoxyglucose FDG activity at these early time points – both large increases and large decreases, which meant that the response to immunotherapy was happening very quickly.

How does imaging at 1 week address challenges associated with later imaging intervals?

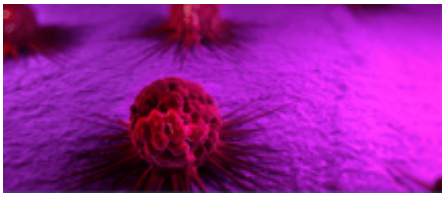
Imaging at 1 week has several advantages compared to imaging at later time points:

- It provides data on what is happening in tumors at a time point that is close to the peak immune response, in which we see these large increases and large decreases in FDG activity, instead of looking later on when the immune response is largely finished. This not only informs patient care but also has the potential to help us better understand immunotherapy response and tumor biology. For example, it was very interesting to see how the kinetics of response varied both between patients and also between different lesions in the same patient, and we have a lot to learn about what these differences in kinetics mean.
- Imaging at 1 week provides very little time for nonresponding tumors to grow, which makes for a much cleaner analysis. At later time points growing tumors typically have increased FDG activity, which can confound the analysis.
- Imaging at 1 week provides an earlier response assessment so patients can potentially change treatment earlier or have more time for additional companion studies (blood tests or additional imaging studies) to inform their response status.

Could you discuss the key findings regarding metabolic flare (MF) and metabolic response (MR) observed in the study, and how these were correlated with treatment response and overall survival?

We found that any large changes in FDG activity (either a metabolic flare or metabolic response) within tumors at 1 week predicted response to immunotherapy. It was exciting to see that these large metabolic changes were only seen in responding patients, so this "MF-MR group" had an objective response rate of 100%. Thus, we were able to identify responding patients with very high confidence. This approach also identified a cohort of patients with stable metabolism which was enriched in nonresponding patients, but more work will need to be done to more accurately identify all of the non-responding patients – either with companion blood tests or additional imaging studies. I will note that we were largely expecting to see increases in FDG activity due to infiltration of activated immune cells and were surprised to see such large metabolic responses (with decreased FDG activity) at 1 week – since this implies that the immune response is happening very quickly.

Also, biomarkers of response to immunotherapy need to not just predict response – they need to be correlated with survival. So it was exciting to see that there was a correlation between these large metabolic changes and survival.



Pulmonary metastatic melanoma: current state of diagnostic imaging and treatments

This review article looks into the current clinical modalities with a focus on diagnostic imaging and therapeutics for pulmonary metastatic melanoma.

What steps are needed for validation of this approach and how would you like to see it integrated into routine clinical practice?

We first need to validate this approach in a larger cohort, and plan to also include combination immunotherapies, which are commonly used in clinical practice. We are also planning on evaluating this approach in patients with NSCLC treated with immunotherapy, and it has the potential to be applied across other cancers and immunotherapy regimens, including cellular therapy.

Since this approach uses FDG PET/CT scans, which are widely available, and we are measuring changes in SUVmax, which are routinely reported in clinical reads, we expect that this approach could be readily applied to routine clinical practice to assess early response to immunotherapy. Responding patients could de-escalate therapy, for example in the neoadjuvant setting by avoiding surgery, and nonresponding patients could change to a different therapy. Although our confidence in identifying non-responders is lower, we would still have the potential to start patients on monotherapy and escalate patients with stable metabolism (which are enriched in non-responders) to combination therapy. But I am confident that we will develop the tools to identify nonresponding patients with much greater confidence in the future, which will enable more options for treatment changes.

Interviewee profile:

Dr. Michael Farwell is an Associate Professor of Radiology at the University of Pennsylvania. He received his MD from Columbia University, is board-certified in Diagnostic Radiology and Nuclear Medicine, and he holds a master's degree in Organic Chemistry from Harvard University. Farwell's research focuses on oncologic applications of molecular imaging, with an emphasis on developing new imaging tools for the rapidly growing field of cancer immunotherapy. He is particularly interested in the development of new methods for imaging the immune response to cancer immunotherapy and tracking cellular therapies via PET. Farwell is co-Chair of the ECOG-ACRIN Immuno-Oncology Working Group and he is the Imaging Chair of the ECOG-ACRIN Melanoma Committee.

Does that MDS diagnosis need a second opinion? An interview with Mikkael Sekeres

A recent study led by Mikkael Sekeres, Chief of Hematology (Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, CA, USA), has demonstrated that blood cancers known as myelodysplastic syndromes/neoplasms (MDS) are commonly misdiagnosed, putting patients at risk for treatment mistakes and other potentially harmful consequences. The findings were recently published in Blood Advances. In this interview we provide you with a breakdown of key points of the research.

In what ways can misdiagnoses of MDS lead to suboptimal treatment decisions?

MDS is a tricky cancer to diagnose, as the diagnosis depends on accurate analysis of cell morphology, immunophenotyping, and genetics. The wrong diagnosis can lead to patients being undertreated, for example if MDS is mistaken as a vitamin deficiency, or overtreatment, if the opposite occurs – if a benign condition is mistaken for MDS.

How do errors in population-based estimates of MDS incidence and mortality occur due to misdiagnosis and what implications do these errors have for both clinical practice and public health planning?

When misdiagnoses occur, population estimates in disease. – in registries such as SEER or cancer registries – can miss the mark, and either overestimate or underestimate population incidence rates and prevalence. This, in turn, affects allocation of appropriate resources to treat conditions such as MDS, and survival estimates. In the case of MDS, we believe these population registries underestimate both the incidence and prevalence of MDS, and the impact of the disease on healthcare resource use. For example, patients with MDS, who tend to have anemia or low platelet counts, use a disproportionate amount of blood products.

Given the effects associated with misdiagnosis of MDS, what strategies or improvements could be implemented to enhance the accuracy of initial MDS diagnoses. Also, how can healthcare professionals work together to minimize the occurrence of misdiagnoses and subsequent negative outcomes for patients?

We need to do a better job in education patients that, for rare bone marrow cancers such as MDS, a second opinion is a must – and that second opinion includes both a meeting with a clinical expert to help guide treatment recommendations, and a second opinion about the diagnosis, from a pathologist, to ensure that the diagnosis is accurate.

Interviewee profile:

Mikkael A. Sekeres joined the University of Miami Health System and Sylvester Comprehensive Cancer Center as Chief of the Division of Hematology. He earned his medical degree and a Master's Degree in clinical epidemiology from the University of Pennsylvania School of Medicine (PN, USA). Sekeres completed his postgraduate training at Harvard University, finishing an internal medicine residency at Massachusetts General Hospital and a fellowship in hematology-oncology at the Dana Farber Cancer Institute (MA, USA). He chaired the Oncology Drugs Advisory Committee of the US FDA, has been on the editorial boards for several medical journals, and chairs scientific advisory boards for patient advocacy groups and research funding agencies.

Uncovering the link between cancer disparities and climate change

Hello, and welcome to the latest episode of OC Talks, the podcast from Oncology Central. Today, I'm joined by Dr Kilan Ashad-Bishop, who is a principal scientist at the American Cancer Society and co-founder and Executive Director of STEMNoire. Her work focuses on the intersection between science, health, and society. Thank you for joining us today.

Could you briefly introduce yourself and give us an overview of your career to date?

Absolutely. My name is Dr Kilan Bishop. I am a California girl who made her way out of California to start pursuing biology. That looks like earning my Bachelor of Science from Morgan State University (MD, USA), which is a historically black college in Baltimore, Maryland, and then making my way down the coast to the University of Miami (CA, USA), to earn my PhD in cancer biology.

From there, I started to realize that I wanted to be more in the community than I wanted to be in the mouse room, even though I really liked the wet lab science and bench science. So, my training started to reflect that. I did some studying in education, in human development, and then cancer disparities and equity and kind of now pulled from all of those experiences and work as a cancer epidemiologist at the American Cancer Society. That's been really cool. It's an extension of my work looking at socio-environmental determinants of cancer disparities I work on the cancer risk factors and screening team looking at behavioral risk factors like tobacco use and obesity, as well as cancer screening participation.

Could you explain the link between cancer disparities and climate vulnerabilities?

Essentially, we have — because of the way that our society, I mean, I could say American society is set up, however, these same things are present in different societies globally, we have systems that are set up that do not serve all people equally. Therefore, disparities in cancer and other health conditions come about because these systems are set up to be unequal, which is going to distance people from things like health care.

It's going to put people in close proximity to tobacco outlets and that's before we even get to the predatory marketing of tobacco, in communities like mine, African-American communities. So you have all of these inequities in society, that coalesce to create cancer disparities and many of those same things coalesce to render communities of color as well as low-income communities, disproportionately vulnerable to the negative effects of climate change. You have communities where there's historic disinvestment, you don't have a lot of greenery.

Then as the world gets hotter and hotter and hotter, the heat is concentrated in those communities. Those may be the same communities where because of the lack of greenery, you don't have as much neighborhood walkability leading to less physical activity, which is a risk factor for cancer. So it's like talking in circles because you start to realize that a lot of these things that create vulnerability to one thing also create vulnerability to another thing and that's that relationship at its base between climate and cancer.

[How does air pollution trigger cancer in non-smokers?]

Discover the mechanism by which tiny pollutant particles may trigger lung cancer in individuals who have never smoked.

There's also been an extremely salient body of work, actually an important body of work emerging to look at the effects of climate-related disasters, on access to health care, on continuity of treatment. Work by Leticia Nogueira, who also is at the American Cancer Society, has found links between wildfire smoke exposure and cancer mortality. So there are really implications for climate change across the cancer continuum from prevention and control, all the way to mortality and survivorship.

What downstream impact does this have on access to screening (including prevention and diagnostics) and treatment options for cancer patients?

When you're thinking about climate change, sometimes it's easy to think about it as something that won't have effects for 20–30 years.

A lot of the ways that we talk about climate focuses on long-term impacts but even if you take that lens, there are environmental exposures and disparities in environmental exposures that have been documented for decades. So then today is when we should be looking. In the US, that plays out in places like Cancer Alley in Louisiana, where you have a really strong concentration of environmental pollutants, and that was on purpose.

Then you see increases in cancer incidence and, unfortunately, in those areas, you don't always see the appropriate level of investment in screening campaigns, and education and outreach campaigns to let people know that because they are at greater risk, they may want to make sure that not only that they are up-to-date with screening, but even seek additional care. It's kind of like, if you see something, say something, right? So there's a downstream effect that's indirect where we have screening guidelines, there are several different sets of screening guidelines in the United States and globally for different types of cancers but those are often not related to an individual's level of risk. The screening that correlates to your level of risk is something that you can really only work out with your doctor if you have the usual source of care, which many people don't.

That's how we get those disparities in people knowing when they're eligible, people knowing when they're up-to-date, and people knowing that sometimes even if you're up-to-date that still warrants an additional checkup or an additional interface with the healthcare system if something comes up.

You recently took part in a roundtable discussion titled Black in Cancer Research and Oncology. What were the key takeaways?

I think some of the key takeaways from that panel were the fact that, firstly, every person who participated has a personal story, and that personal story is reflected in their research and advocacy work.

I think so often as scientists we're told that, like, science is something objective, and so theoretically we should all be doing science, conducting science, or interpreting science the same way. But that's not real. That's not real life.

We all have different identities and stories, and they affect the way that we work. And sometimes they can affect the way that we work in really positive ways, in ways that expand the ways that we approach inquiry and like I said, interpretation of those results.

The other key takeaway was just that sometimes, representation or the presence of black voices, is not enough. It's the volume of black voices that has to be accounted for. So in many of the training environments that exist for people to become in a formal sense, real scientists, with my air quotes, there's not always space to voice what ways you are comfortable or uncomfortable, with the material being imparted to you, space to feel like maybe you have an opportunity or not to push back on certain things that are being taught or to ask those additional questions that are really influential to training.

So, there was a shared desire to raise the volume of black voices, not only in formal training environments but also as we think about community education and outreach to have a workforce that is reflective of the people who are the most burdened by cancer and other chronic diseases, so that we can really start to make our way to rebuilding some trust in medical care and our health care systems and start to address these disparities.

Is that where your motivation came from to start STEMNoire?

Yes I co-founded STEMNoire in 2019 with another scientist Teressa Alexander, who I met at Morgan State. Now, I'm a biologist, she's way smarter than me, she's a physicist. And, I'm an American Black woman, she was an international student from Trinidad and Tobago.

Despite the fact that we had these really different backgrounds and really different research interests, as we stayed in touch and stayed friends and went into different training environments and earned different degrees, we started to see that the similarities were just way more prominent than the differences, in the ways that we felt in certain environments and the things that we honestly felt that we were lacking in certain environments.

So we created STEMNoire because we wanted to have a space that was curated for us, and by us, to not only enhance our professional outcomes, which you find a lot of support for but also to enhance our personal well-being in a holistic way, so that we're not in the room at the expense of ourselves.

Can you tell us about the upcoming STEMNoire conference?

Absolutely. So just to go back, STEMNoire is a research and wellness community for Black Women in Science, Technology, Engineering and Math. We serve a global community of approaching 2,500 women.

We're really proud that we've been able to bridge those different geographies and fields, training and experiences. To date, we've hosted three conferences, two virtual, and one in person in San Juan, Puerto Rico. For STEMNoire 2024, which is June 20–23rd 2024, we will be in Washington D.C. (USA). We're excited to bring together our community for a phenomenal lineup of keynote speakers, personal and professional development workshops, as well as research presentations and opportunities to network and collaborate.

We have all of that information after STEMNoire 2024 on our website, which is stemnoire.org. Or you could find us on social media for a little more of the fun stuff.

What concept in oncology research are you most excited about?

That's a really good question. I'm really interested in bodies of work that look at intersectionality in oncology outcomes. I have a mentor who is a vanguard in structural racism and considering how structural racism patterns health disparities — but I'm a black woman, so, yes, it's racism, but it's also sexism and misogyny and patriarchy. Then there are also people who deal with discrimination based on nationality. There are also people who deal with discrimination based on sexual and gender identity.

I'm really excited about people who are creating innovative ways to study outcomes at the intersection of people's identities, and about the work to create interventions that are highly personalized to communities in which we have seen persistent health disparities, so trying something new and exciting.

Interviewee profile:

Dr Kilan C. Ashad-Bishop (she/her) is a biomedical scientist and advocate for inclusion working at the intersection of science, health, and society. She is a proud alumna of Morgan State University, where she earned her Bachelor of Science in Biology, and the University of Miami, where she earned her Ph.D. in Cancer Biology. Currently a Principal Scientist at the American Cancer Society, Kilan focuses her transdisciplinary research and service portfolio on the influence of social and environmental factors on cancer disparities.

Guided by a strong belief in the transformative power of equity and inclusion in health, science, and society, Dr Ashad-Bishop champions the responsibility of science (and scientists) in driving positive social change. In 2019, she co-founded STEMNoire, a research and wellness community that supports and empowers Black women in STEM. With a global reach, STEMNoire has rapidly expanded to serve a vibrant community of 2,500 Black women in STEM education and the workforce, providing resources for holistic wellness, collaborative networking, and personal and professional development.

Beyond her professional pursuits, Kilan finds joy in spending time with her pets and tending to her thriving collection of houseplants. Additionally, she cherishes moments spent in nature and the gym.

Short Communication

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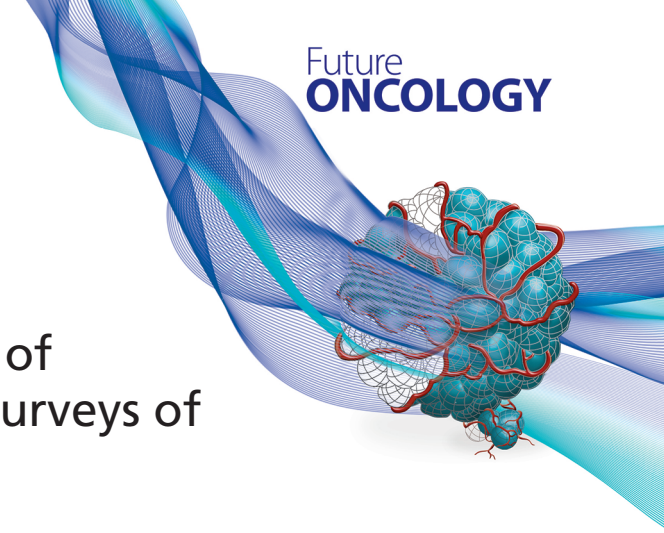

Diagnostic journey and life impact of cholangiocarcinoma: results from surveys of patient and caregiver experiences

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Aim: To understand cholangiocarcinoma symptoms, diagnosis and treatment experience from the patient and caregiver perspective, including cholangiocarcinoma's impact on daily life, quality of life (QoL) and mental health. **Methods:** Patients and caregivers participated in two online surveys (in partnership with the Cholangiocarcinoma Foundation). **Results:** The patient survey data (n = 707) show a substantial impact of cholangiocarcinoma on QoL and mental health, with 34% of patients reporting symptoms consistent with moderately severe/severe depression. The caregiver survey data (n = 60) show that although caregivers experience satisfaction in their role of caring for a loved one, managing the demands of caregiving exacts a physical, mental and emotional toll. **Conclusion:** These surveys highlight the need for better palliative and supportive care interventions.

Plain language summary:

What is this article about?: It shows results from two surveys, one for people with cholangiocarcinoma (CCA, pronounced kō·lan·jee·ō·car·sin·nō·muh), and one for caregivers (people who take care of family or friends with CCA without payment). CCA is a rare and aggressive cancer. The caregivers we surveyed were not necessarily taking care of the people with CCA who we surveyed. We did the surveys to find out how CCA changed the lives of people in these two groups.

What were the results?: We surveyed 707 people with CCA. Patients reported in the survey that having CCA impacted their daily lives in lots of ways. Most needed help with daily chores like housekeeping and shopping. Both tiredness and anxiety were reported by about two in three people with CCA. More than one in three had said they had symptoms indicating potential depression, which means patients should have their mental health evaluated. CCA also reduced their sexual desire and intimacy with their partner.

We surveyed 60 caregivers who reported both good and bad experiences taking care of a person with CCA. The good experiences included knowing that their loved one was well cared for and learning to deal with difficult situations. Many caregivers also felt closer to their loved one with CCA. The bad experiences included exhaustion and emotional and mental stress. Caregivers felt challenged by trying to understand CCA and the treatment options available.

What do the results of the study mean?: Patients with CCA and their caregivers need more help and support.

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Keywords: burden • caregiver • cholangiocarcinoma • mental health • quality of life

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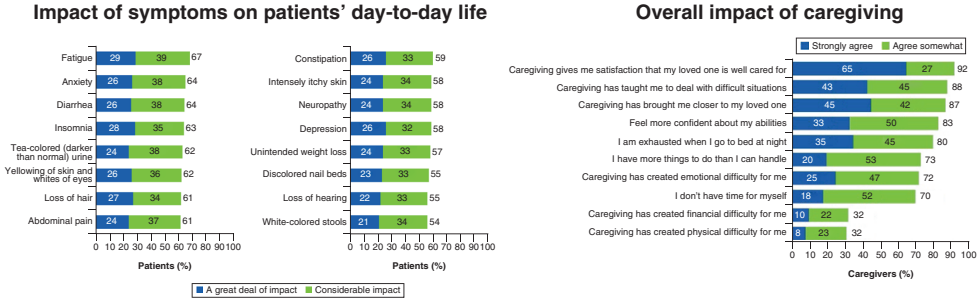
Graphical abstract:



Cholangiocarcinoma (CCA) is a rare cancer arising from the biliary tree. Based on the anatomical site of origin, CCA is categorized into intrahepatic CCA and extrahepatic CCA, the latter of which is further classified into perihilar and distal CCA [1]. In the USA, approximately 8000 people are diagnosed with CCA each year [2]. A study of Surveillance Epidemiology and End Results registry data found that between 2001 and 2017, the incidence of CCA increased from 3.08 to 4.43 per 100,000 [3]. The majority of patients (67%) were ≥65 years of age at CCA diagnosis, but the largest percentage increase in the incidence of CCA was reported in younger patients (18–44 years) [3].

Patients with CCA typically present in advanced stages, owing to the aggressive nature of the disease and the fact that the disease can be largely asymptomatic at early stages [4]. Moreover, CCA may be misdiagnosed as another adenocarcinoma, including cancer of unknown primary, owing to a similar histopathology and clinical presentation [5], a paucity of diagnostic markers specific to CCA [6]; thus, CCA is commonly a diagnosis of exclusion [7]. Consequently, CCA is often associated with a poor prognosis [8,9]. In common with other malignancies [10,11], patients with advanced biliary tract cancers including CCA have a decreased quality of life (QoL) with multiple domains of their daily living impacted due to disease-related and treatment-related factors [12–14]. In patients with CCA, commonly reported symptoms that impact their QoL include jaundice, abdominal pain, nausea, fatigue, unintended weight loss and fever [4,15,16]. In a single-center prospective study that assessed QoL in 133 patients with CCA [13], patient-reported QoL showed a general decline with a significant decrease in emotional functioning and financial difficulties after 6 months of treatment.

Caregiving for patients with debilitating diseases, including cancers, can be burdensome [17]. Owing to the disease, treatment side effects and/or other comorbidities, patients with advanced cancers not only need physical support and emotional care, but may also require assistance with basic daily tasks [17,18]. The caregiver role therefore can be demanding and cause substantial burden in various domains of life, including their physical, emotional, and mental health and their overall QoL [19–21]. Ultimately, this can affect the quality of care provided by caregivers.

Real-world studies collect data outside of clinical trials in the context of routine delivery of care. As such, data from these studies may be more representative of real-world patients and outcomes for certain measures, such as QoL, than clinical trials which have strict eligibility criteria [22]. Data from real-world studies can, therefore, complement and increase the generalizability of data from clinical trials. To date, few real-world studies have assessed the QoL of patients with CCA [13,23,24]; except for a study that assessed the QoL of caregivers in Northeastern Thailand [25], the experience of caring for a patient with CCA and the impact on the various domains of a caregiver's life remain largely unexplored. The lack of knowledge of the impact of CCA on QoL, including physical, mental and emotional aspects, can affect the clinical and palliative management of patients with CCA. Identifying and quantifying both the patient and the caregiver experience of CCA can help to develop more tailored interventions, and provide the support, services and outreach that can help preserve their QoL.

This article reports data from two separate surveys, one focused on the burden that CCA exerts on patients and the other focused on understanding the caregiver's experience of caring for a patient affected by the disease. The objectives of the patient survey were to understand the diagnosis experience, determine the disease burden and describe the QoL and psychosocial impacts of CCA. The caregiver survey assessed the impact of caregiving on the day-to-day life and QoL of caregivers.

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Methods

Study design & QoL assessments

Patients with CCA and caregivers of patients with CCA were recruited in partnership with the Cholangiocarcinoma Foundation (CCF) to participate in two separate online surveys to evaluate the disease burden on both patients and caregivers. The study was advertised on the CCF website and social media, including a link requesting contact information for those interested in participating. Subsequently, an individual single-use link was sent to each interested participant. Each participant completed the survey screen to determine whether they met the eligibility criteria to participate in the survey. Eligibility was determined by responses to screening questions in the surveys. Patients and caregivers were required to be aged ≥18–years and reside in the USA. Patients had to confirm that they had been diagnosed by a medical doctor with one or more of biliary tract cancer, bile duct cancer, or cholangiocarcinoma; patients with ampulla or gallbladder cancer were excluded. Caregivers were required to have currently or previously provided unpaid care to a family member or friend with CCA (biliary tract cancer/bile duct cancer); caregivers were excluded if the person they provided care for also had two or more of the following cancers: gallbladder cancer, liver cancer, ampullary cancer or lung cancer. Participants who met the screening eligibility then were asked to respond to the survey questions. To opt-in to participate and receive the financial incentive for participation (a US$25 gift card), the participants were required to provide their real names and, whenever possible, the CCF patient and caregiver registry was used to verify the identity of patients/caregivers. It should be noted that the caregivers surveyed were not necessarily the caregivers of the patients surveyed. Informed consent was obtained electronically from all patients and caregivers who participated in the study.

The 30 min patient survey was conducted between 23 August 2019 and 20 September 2019. Participating patients were stratified by self-reported stage of CCA into stage 1–2 (early stage), stage 3a (may be able to have surgery), stage 3b (probably cannot have surgery), stage 4 (cancer has spread to another organ), 'in remission, no evidence of disease' or 'don't know'. The survey assessed demographics, disease staging, symptoms, diagnosis/treatment experience, impact on day-to-day life, QoL and mental health. The survey included the European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire-BIL21 (EORTC QLQ-BIL21), a validated tool for assessing the QoL of patients with CCA [16]. The EORTC QLQ-BIL21 comprises 21 questions that include several subscales of interest, namely eating, jaundice, tiredness, pain, anxiety, treatment side effects, difficulties with drainage bags/tubes and concerns about weight loss [16]. The EORTC QLQ-BIL21 scoring was calculated on a scale of 0–100 [16]. Screening for depression was conducted using the Patient Health Questionnaire-9 (PHQ-9) [25], which is a nine-item self-reported questionnaire. The PHQ-9 score can range from 0 to 27, with each of the nine symptoms individually scored from 0 (not at all) to 3 (nearly every day). Overall scores of 0–4, 5–9, 10–14 and 15+ indicate no/minimal, mild, moderate and moderately severe or severe depression, respectively. An appended item to the PHQ-9 asks patients "How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?" [25]. The Work Productivity and Activity Impairment questionnaire [26] was used to assess the impact of general health and disease symptoms on work impairment, absenteeism, presenteeism and daily activity impairment. Data are presented as a percentage from 0% (no impairment/productivity loss) to 100% (maximal impairment/productivity loss). Patients were also requested to indicate their considerations in making treatment decisions as part of the survey. Eleven pre-specified options were presented in a randomized order (see Figure 1C) and patients could also select that they considered 'other' considerations and provide details as free text. Patients who selected more than one consideration were then asked to specify the consideration they considered to be of greatest importance from a list of previously selected responses which were presented in the same order as before.

The 25 min caregiver survey was conducted between 1 September 2021 to 8 December 2021. Caregivers were stratified by self-reported disease stage of patients into early stage (stages 1, 2, 3a), later stages (stages 3b, 4), 'CCA patient passed away', 'in remission, no evidence of disease' or 'don't know'. The PHQ-9, Caregiver Burden Inventory (CBI) and the Caregiver Burden Scale (CBS) were used to assess the physical, mental and emotional burden of caregiving. The CBI is a diagnostic tool that includes 24 items across five dimensions of caregiver burden, namely physical health, time dependency, social relationships, personal development and emotional health [27]. Each item in each dimension is given a score between 0 (never) and 4 (nearly always), with higher scores indicating greater caregiver burden. Total summary score for the five CBI dimensions can range from 0 to 100 [27].

To assess the perceived burden among caregivers due to patient tasks requiring assistance, the CBS was used [28]. In addition to the original 15 items (housekeeping, shopping, transportation, cooking, decision-making, yard

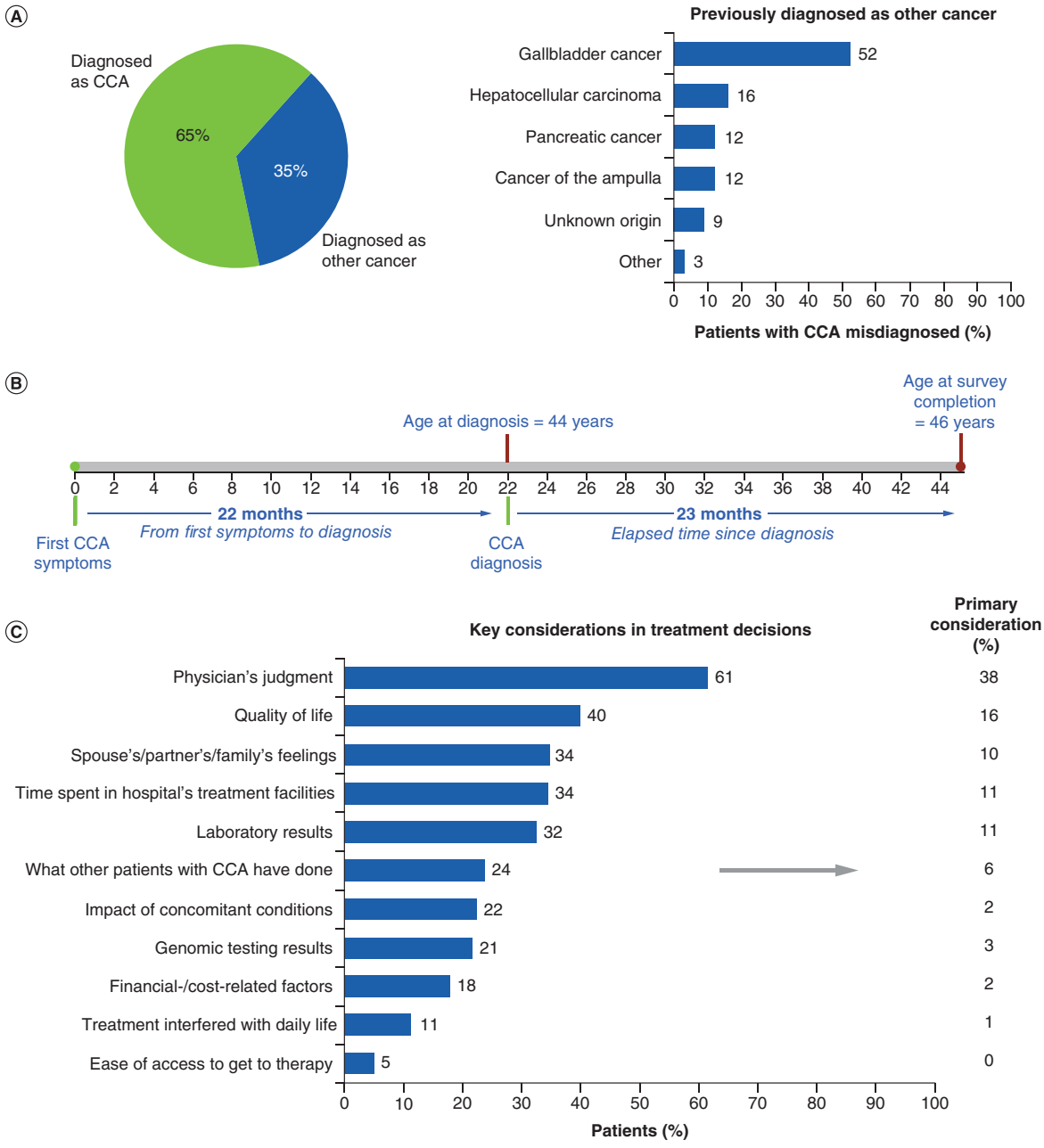

Figure 1. Patient diagnostic journey. (A) Initial misdiagnosis is frequent; **(B)** patient diagnosis journey timeline; **(C)** key considerations in treatment decisions. In panel B, mean values are reported.
CCA: Cholangiocarcinoma.

work/farming, making household repairs, administering medication, financial record-keeping, walking, eating, dressing, bathing, leaving patient unattended and toileting) in this scale, 'childcare (Y/N)?' and 'other task (Y/N)?' items were added.

Caregiver task assistance was determined by the number of tasks for which the patient needed assistance and the caregiver provided assistance. Perceived burden was assessed as the number of tasks for which the patient needed assistance and the caregiver provided assistance and which the caregiver reported as adding to personal stress [28]. For each domain assessed, the possible range was from 0 to 17.

Table 1. Patient demographics.

Variable, n (%)	Total patients (N = 707)	Current stage†			
		Stage 1–2 (n = 157)	Stage 3a (n = 364)	Stage 3b–4 (n = 140)	Remission (n = 30)
Age, years					
<45	259 (37)	69 (44)	118 (32)	53 (38)	9 (30)
45–54	353 (50)	53 (34)	203 (56)	75 (54)	18 (60)
≥55	95 (13)	35 (22)	43 (12)	12 (9)	3 (10)
Sex					
Men	541 (77)	129 (82)	285 (78)	101 (72)	17 (57)
Education					
High school or less	196 (28)	28 (18)	118 (32)	43 (31)	6 (20)
Some college	340 (48)	103 (66)	146 (40)	66 (47)	16 (53)
College graduate or higher	170 (24)	26 (17)	100 (27)	31 (22)	7 (23)
Currently employed					
Yes	554 (78)	118 (75)	286 (79)	104 (74)	30 (100)
No	153 (22)	39 (25)	78 (21)	36 (26)	0
Marital status					
Single	9 (1)	3 (2)	3 (1)	3 (2)	0
Divorced or separated	29 (4)	6 (4)	15 (4)	5 (4)	2 (7)
Widowed	5 (1)	0	5 (1)	0	0
Married/living with partner	661 (93)	148 (94)	340 (93)	132 (94)	27 (90)
Income, $USD					
<50,000	58 (8)	12 (8)	26 (7)	14 (10)	6 (20)
50,000–74,999	238 (34)	101 (64)	100 (27)	25 (18)	7 (23)
75,000–99,999	288 (41)	31 (20)	166 (46)	78 (56)	7 (23)
≥100,000	112 (16)	11 (7)	70 (19)	22 (16)	7 (23)
Medical insurance					
Private insurance	207 (29)	53 (34)	99 (27)	37 (26)	9 (30)
Medicare	348 (49)	57 (36)	202 (55)	70 (50)	12 (40)
Medicaid	134 (19)	38 (24)	59 (16)	30 (21)	7 (23)
Other medical insurance	17 (2)	9 (6)	4 (1)	3 (2)	1 (3)

† 16 patients reported their disease stage as unknown.
Percentages may not total 100 owing to rounding or incomplete responses.

Statistical analyses

All respondents were included in the analyses; data from patients and caregivers were analyzed separately. Data were summarized using descriptive statistics. Two-sided test was used to determine statistical significance; observed p-values were assessed at $\alpha = 0.05$ level for statistical significance, with no multiplicity adjustment. For all comparisons of means, a pair-wise t-test was performed, and independent z-tests were used for comparisons of percentages. Patient- and caregiver-reported data analysis was performed using SAS® statistical software, version 9.4 (SAS Institute, Cary, NC, USA). Missing data were not imputed.

Results

Patient survey

Patient demographics & diagnostic journey

Of the 1286 patients invited, 707 (55%) completed the survey, of whom 50% were 45–54 years of age; 77% of patients were male (Table 1). There were 157 patients with stage 1 or 2 CCA, 364 with stage 3a CCA, 140 with stage 3b–4 CCA and 30 in remission; 47% had perihilar CCA, 41% had intrahepatic CCA and 12% had distal CCA.

Initial misdiagnosis was reported by 35% of patients (n = 247); the most common prior diagnosis was gallbladder cancer (52%; Figure 1A). 52% of patients indicated that they had sought multiple opinions from different oncologists after they received a diagnosis of CCA; patients consulted a mean of 2.5 oncologists. The mean age at

CCA diagnosis was 44 years; the mean duration from CCA symptom onset to diagnosis was 22 months; and the mean duration from CCA diagnosis to survey completion was 23 months (Figure 1B). Among key considerations for patients in making treatment decisions concerning their primary medical therapy, the most common was physician judgment (61%; primary consideration in 38%), followed by QoL (40%; primary consideration in 16%; Figure 1C). A comparison among patients with different stages of CCA was also performed; significantly more patients with late stage CCA (Stage 3b-4, 17%) were likely to give the highest consideration to time spent in hospitals/treatment facilities compared with those with early stage CCA (stage 1–2, 6%; stage 3a, 10%; $p < 0.05$). Also, a higher percentage of patients with stage 3b-4 CCA (23%) gave QoL after treatment the greatest importance in treatment decision compared with patients with stage 1–3a CCA (14%; $p < 0.05$).

Impact on day-to-day life & QoL

All patients reported experiencing at least one symptom potentially associated with CCA. Of 16 symptoms in the survey, patients reported that a mean of 13.8 symptoms had an impact on their daily life. Fatigue was the most commonly reported symptom, with 67% of patients indicating having a "considerable" or "great deal of" impact on daily life (Figure 2A). As assessed using the EORTC QLQ-BIL21, patients overall reported a substantial negative impact of CCA on QoL, with mean scores ranging from 48.9 to 52.9 on all domains. On the same scale, younger patients (18–44–years of age) reported higher mean QoL scores across all domains except weight loss compared with older patients (>45–years; Figure 2B). Overall, 98% of patients reported any impact of CCA on their work status, and 37% reported considerable impact or great deal of impact on work status.

Using the Work Productivity and Activity Impairment questionnaire, the 554 patients (78%) who reported that they were currently employed and had worked in the past 7 days, reported a mean of 16.5% of work time lost. Mean reported impairment while working (presenteeism) was 65.3% and mean overall work impairment was 70.4%.

Impact on patient mental health & sexual function

Based on PHQ-9, 34% of patients (39% with stage 3a CCA) reported symptoms consistent with moderately severe or severe depression (Figure 3A). Overall, 42 to 51% of patients experienced any given individual symptom of depression nearly every day or more than half of the days (Figure 3B). Furthermore, 72 and 23% of patients said symptoms of depression make their daily lives 'somewhat' or 'very difficult', respectively.

Patients were also surveyed regarding impact of CCA on sexual function (Figure 3C). Most patients reported lack of sexual desire (87%) or loss of intimacy (86%); with 51 and 47% reporting a considerable or great deal of impact on sexual desire and loss of intimacy, respectively. Compared with patients with stage 1–2 (48%) and 3a (48%) CCA, a higher percentage of patients in stage 3b–4 CCA (61%) experienced a considerable or great deal of impact on sexual desire. Similarly, a higher percentage of patients with stage 3b–4 CCA (52%) reported a considerable or great deal of impact on loss of intimacy in comparison to patients with stage 1–2 CCA (39%).

Caregiver survey

Caregiver demographics

Of the 109 caregivers invited, 60 (55.0%) completed the survey. Most (85%) were women and 77% were the spouses/partners of their patient with CCA (Table 2). The majority of caregivers were 50–64 years (38%) or ≥65 years of age (38%). At the time of the survey, 73% had been in the caregiving role for less than 2 years and 67% (n = 40) were caregivers for patients with advanced disease (stages 3b and 4). Half of the caregivers reported being employed either full-time or part-time, and 35% reported a household income between US$75,000 and <$150,000.

Impact on emotional & mental health

Most of the caregivers reported several positive aspects to caregiving, citing "satisfaction that loved one is well cared for" (92%), "caregiving has taught me to deal with difficult situations" (88%), "caregiving has brought me closer to my CCA patient" (87%) and "I feel more confident about my abilities" (83%) as personal benefits of caregiving (Figure 4A).

Caregivers also reported negative effects, such as being exhausted at bedtime (80%), having too much to do (73%), caregiving creating emotional difficulty (72%) and not having time for themselves (70%; Figure 4A). Additionally, 95% of caregivers agreed that the worst part of caregiving is the uncertainty of the future and 90% agreed that they avoided planning for future events due to uncertainty of patient health (Figure 4B).

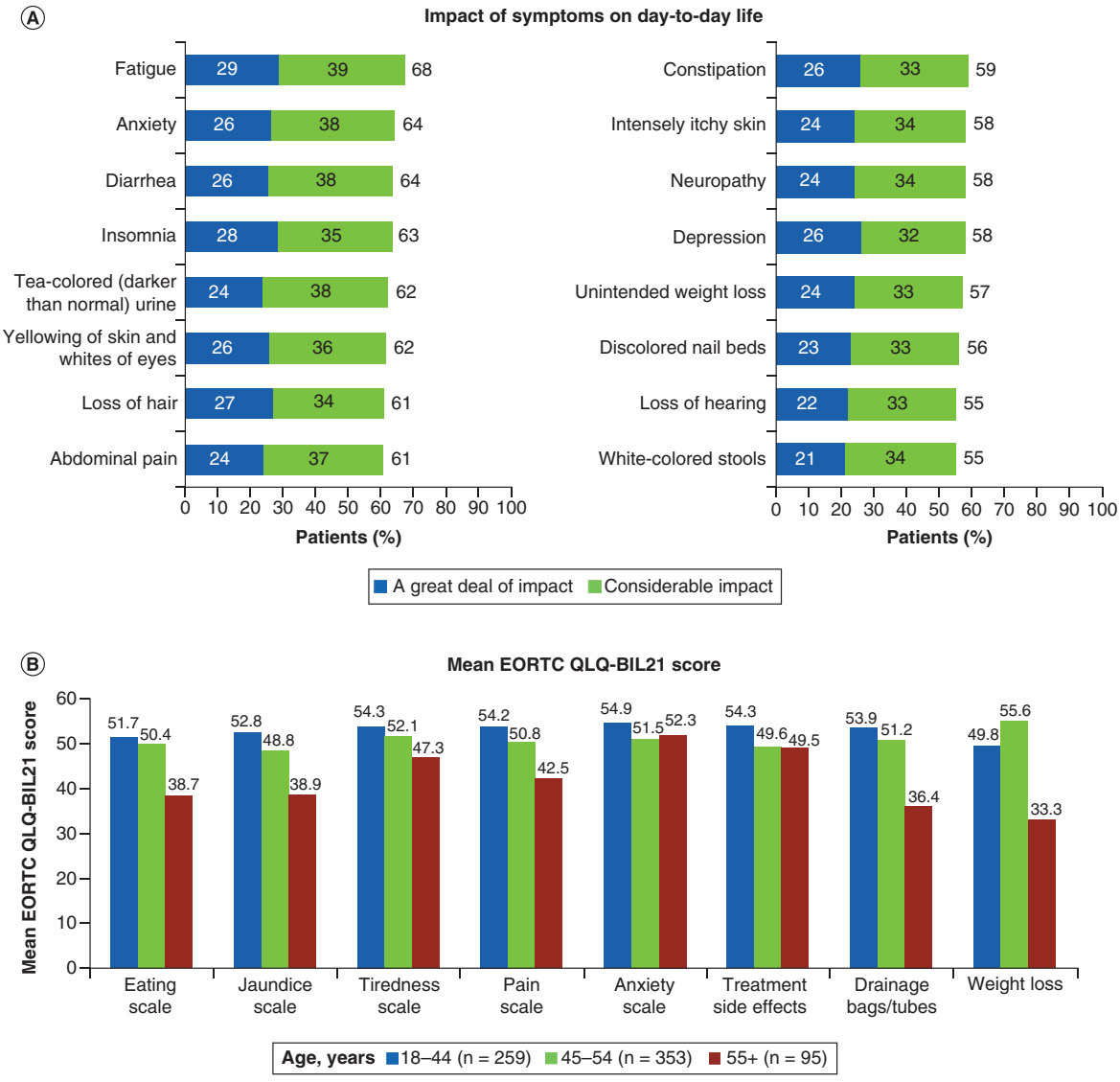

Figure 2. Cholangiocarcinoma impact on quality of life of patients. (A) Impact of symptoms on day-to-day life; **(B)** EORTC QLQ-BIL21 scores across different subscales. In A, owing to rounding, some totals may not correspond with the sum of the separate figures. In B, mean values are shown.
CCA: Cholangiocarcinoma; EORTC QLQ-BIL21: European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-BIL21.

Managing the emotional and mental distress of caregiving was reported by 83% of caregivers as a particularly challenging aspect of caring for a patient with CCA (Figure 4C). Notably, based on PHQ-9 scoring, 73% of caregivers reported symptoms consistent with depression, with 38, 25 and 10% reporting symptoms consistent with mild, moderate and moderately severe or severe depression, respectively (Figure 4D). Most caregivers are managing caregiving stress without professional help. Only 32% of caregivers reported being under the care of a therapist, psychologist, psychiatrist, or other counselor.

To further evaluate caregiver burden, the CBI was used to understand the frequency of feelings across several dimensions of life [27]. The mean overall CBI score was 29.62, reflecting the large numbers of caregivers who sometimes, quite frequently or nearly often felt their CCA patient was dependent on them (80%), were physically tired (75%), felt their social life had suffered (75%), were not getting enough sleep (65%) and had expected things would be different at this point in their lives (80%).

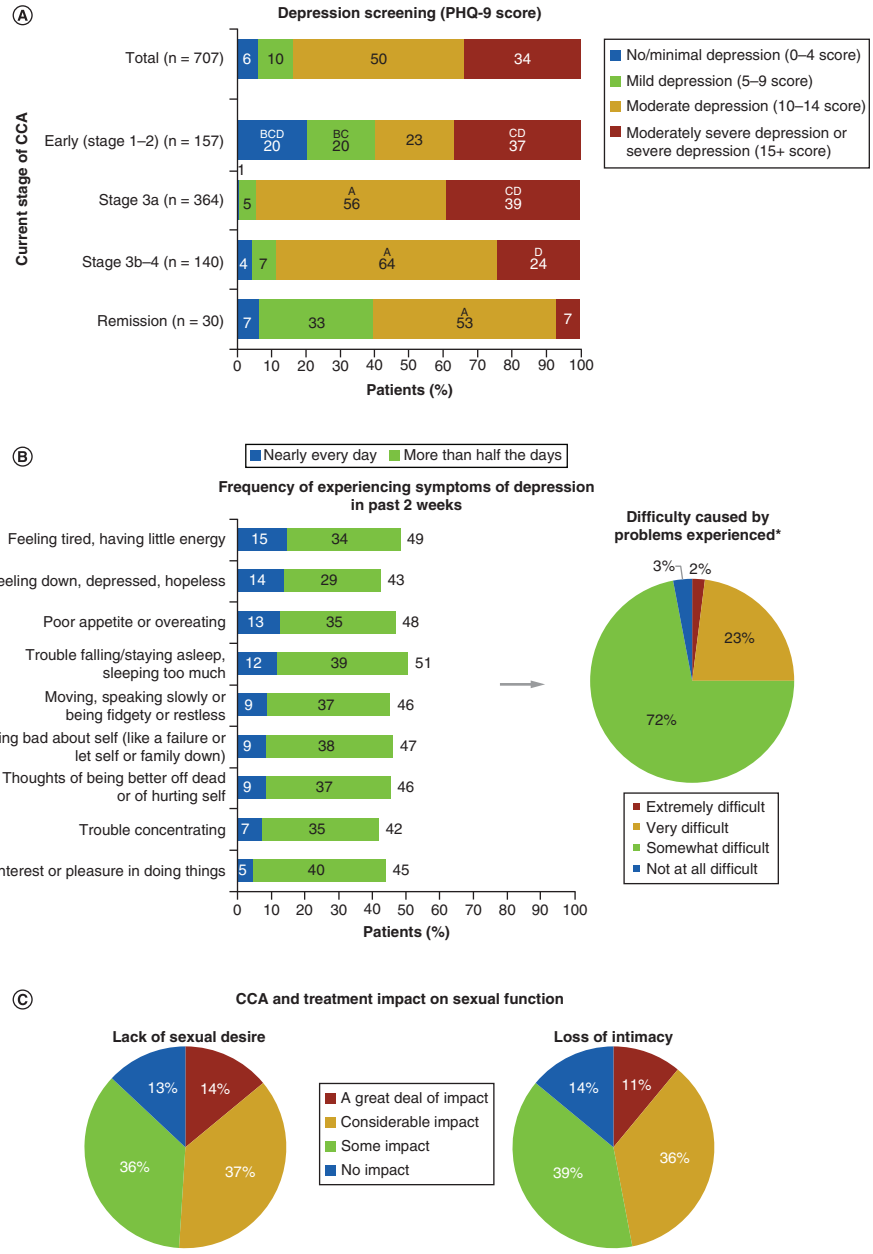

Figure 3. Cholangiocarcinoma impact on patient mental health and sexual function. (A) Depression screening based on PHQ-9 scoring; **(B)** frequency of symptoms of depression and their impact on day-to-day life; **(C)** impact of CCA and its treatment on sexual function. In A, percentages may not total 100 owing to rounding. In B, owing to rounding, some totals may not correspond with the sum of the separate figures. Significant differences are denoted by a superscript letter to next to the higher percentage: **A** = early (stage 1–2); **B** = stage 3a; **C** = stage 3b–4; **D** = remission.
*Among those bothered by any of these problems (N = 707/100%).
CCA: Cholangiocarcinoma; PHQ-9: Patient Health Questionnaire-9.

Caregiving tasks & impact on daily life

Caregiving responsibilities impact daily life. Among those employed full-time or part-time, nearly half (47%) reported a considerable/great deal of impact on their employment. Caregivers allocated on average 38% of their time assisting with patient-related basic functions (such as bathing or preparing meals) and patient-related tasks (such as taking care of bills or running errands). Some caregivers reported that it was it extremely/very difficult to interact with others (32%), do their own work (23%) and take care of things at home (22%; Figure 4E).

Table 2. Caregiver demographics.

Variable, n (%)	Total caregivers (N = 60)	Later stages (3b, 4) (n = 40)
Age, years		
<45	11 (18)	6 (15)
45–54	9 (15)	4 (10)
≥55	40 (67)	30 (75)
Sex		
Women	51 (85)	33 (83)
Patient relation to caregiver		
Spouse/partner	46 (77)	33 (83)
Parent	9 (15)	4 (10)
Other family	4 (7)	2 (5)
Education		
High school or less	6 (10)	3 (7)
Some college	10 (17)	8 (20)
College graduate or higher	44 (73)	29 (72)
Length of time in caregiver role, years		
<2	44 (73)	28 (70)
2–<5	15 (25)	12 (30)
≥5	1 (2)	0
Household income, $USD		
<50,000	4 (7)	1 (2)
50,000–74,999	8 (13)	5 (13)
75,000–99,999	11 (18)	8 (20)
≥100,000	24 (40)	17 (43)
Employment status		
Full-time/part-time	30 (50)	19 (48)
Retired	22 (37)	17 (43)
Not employed	7 (12)	4 (10)
Student	1 (2)	0

Percentages may not total 100 owing to rounding or incomplete responses.

On the CBS, the mean number of tasks the patient needed assistance with, the caregiver provided assistance with, and those that added to the caregiver's personal stress was 8.2, 7.5 and 3.6, respectively. Tasks that require the most assistance included housekeeping, transportation, household repairs, shopping, cooking and decision-making (Table 3).

Discussion

CCA is an aggressive cancer associated with substantial morbidity and poor prognosis. Consequently, the burden of the disease is high, especially for patients with advanced-stage CCA and their caregivers. To our knowledge, this is the first report assessing multiple aspects of CCA disease burden on both patients with CCA and caregivers of patients with CCA. Results from the surveys presented here highlight the unmet needs for supportive care for patients with CCA and their caregivers.

The patient survey analysis shows that the diagnosis journey is often long and arduous, with over a third of patients with CCA being initially misdiagnosed despite experiencing disease-related symptoms for nearly 2 years. Indeed, the absence of CCA-specific symptoms in the early stages of the disease makes the diagnosis difficult. Furthermore, patients with CCA develop significant symptoms only at later stages of the disease [29]. Misdiagnosis and/or late diagnosis may be distressing for both patients and their caregivers.

Although most patients noted that their physician's judgment was the main driver for treatment decisions, the second most frequent response was the impact of treatment choice on QoL. This highlights the fact that QoL remains a key consideration in treatment decisions, despite most patients being diagnosed in later stages of CCA. Several studies assessing patient-reported outcomes have reported psychological distress and physical impairment

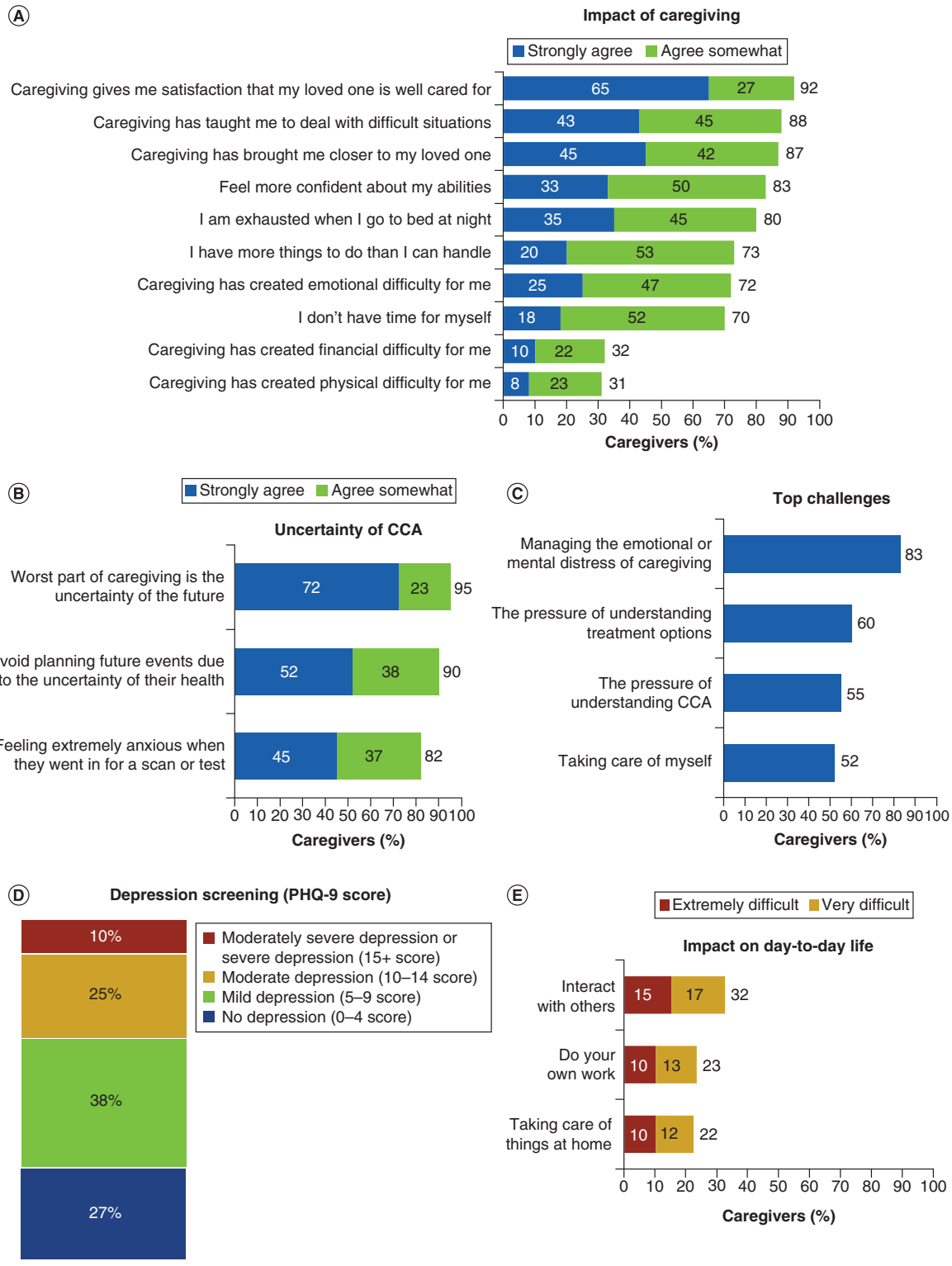

Figure 4. Caregiver burden. (A) Overall impact of caregiving; **(B)** uncertainty of CCA; **(C)** top challenges faced by caregivers; **(D)** depression screening based on PHQ-9 scoring; **(E)** impact on day-to-day life. In panel A, owing to rounding, some totals may not correspond with the sum of the separate figures.
CCA: Cholangiocarcinoma; PHQ-9: Patient Health Questionnaire-9.

Table 3. Tasks requiring caregiver assistance.

	Patient needed assistance (%)	Provided assistance (%)	Task added to personal stress (%)
Housekeeping	82	78	43
Transportation	78	73	22
Shopping	72	72	20
Cooking	68	67	30
Decision-making	65	65	43
Making household repairs	75	60	38
Yardwork or farming	55	48	23
Administering medication	53	53	28
Financial record-keeping	50	50	30
Walking	43	42	8
Eating	30	27	7
Dressing	28	25	7
Bathing	27	22	13
Leaving patient unattended	25	22	20
Toileting	20	15	10
Childcare	5	5	5
Other task	30	23	15

as common among patients with multiple tumor cancer types [30–32], including those with CCA [13,23,24,33]. In common with these studies, our findings from the patient survey indicated substantial impact of fatigue and anxiety due to CCA and its treatment on daily lives, QoL, work productivity and mental health. Our study therefore bolsters the understanding that physical and mental distress are prevalent symptoms among patients with CCA.

In addition to anxiety, depression appears to be a major psychological challenge for patients with CCA, which impacts on their QoL. In this survey, over a third of patients reported symptoms consistent with moderately severe or severe depression. These findings are similar to another study [23] of 23 patients with early, locally advanced or metastatic biliary tract cancer, 17 of whom reported having an emotional impact (depression), suggesting the need for mental health supportive care for patients with cancer.

Our survey results also show that younger patients reported better QoL scores in most domains measured on the EORTC QLQ-BIL21. As previously observed in patients with other cancers [34–37], this may be because older patients often have several confounding factors that are age-associated, such as comorbidities, changes in daily life activities, circumstances and increased susceptibility to treatment toxicities, all of which have a negative impact on the QoL. Further research and analyses toward understanding this observation in young versus old patients with CCA will help develop suitable supportive therapies.

Another observation that emerged from the patient survey was the large impact that appearance-related symptoms such as loss of hair and unintended weight loss had on the daily lives of patients. To our knowledge, this is the first time these specific aspects affecting the patient's life have been evaluated. These observations highlight the need for including suitable interventions such as educational sessions to better inform patients with CCA treatment side effects and symptom-management.

Employed patients who had worked in the past week had overall work impairment of 70%. This is consistent with the upper range of overall work impairment values (40–72%) that were reported in a systematic review [38] evaluating the effect of treatment for multiple cancer types on work productivity in patients and their caregivers. A retrospective cohort study using administrative claims data for patients with CCA found substantial productivity loss due to days missed from work [39]. The mean number of days absent for illness per patient per month was 6.0 and 4.3 days for patients with intrahepatic and extrahepatic CCA, respectively. The mean number of days per patient per month on CCA-related short-term disability leave was 6.5 and 4.3 days for patients with intrahepatic and extrahepatic CCA, respectively [39].

We surveyed patients on sexual function and confirmed a considerable or great deal of impact of CCA and its treatment on sexual desire and intimacy. The impact of cancer diagnosis and treatment on sexual function can be substantial and may worsen with time if not addressed [40]. Therefore, healthcare professionals should discuss sexual functioning with their patients to improve QoL. The American Society of Clinical Oncology also provides

recommendations and guidelines to help the patient's healthcare team address sexual problems arising due to cancer and/or treatment [41].

The majority of caregivers of patients with CCA in the present survey were women, consistent with what is seen with other cancer types [19,42]. In this study, most caregivers were a patient's spouse and many were employed. Caregivers do experience positive aspects throughout the course of caregiving for their loved ones, such as strength to deal with adversity, improved sense of self-worth and increased closeness with the patient [20,43]. In our study, over 80% of caregivers reported that caregiving brought satisfaction that their loved one is well cared for, taught them to deal with adversity and instilled personal confidence. However, caregivers for patients with cancer also experience physical, mental and emotional burdens [19,20,42,44,45]. Likewise, caregivers of patients with CCA reported physical impairment and emotional distress in our survey. The majority of the caregiver respondents reported annual household incomes of US$75,000 or above. Patients with fewer resources may be expected to experience greater burdens.

Work productivity is also affected in caregivers [38]. A systematic review reported overall work productivity loss among caregivers of 21–27% [38]. Because of responsibilities associated with caregiving, caregivers report having to make adjustments at their workplace, such as taking time off, going from full-time to part-time or taking a leave of absence [42]. Caregivers in our survey reported spending over a third of their time on caregiving duties, with nearly a quarter reporting that caregiving made it 'very' or 'extremely difficult' to work. Those who were employed full-time or part-time reported that their employment status had a great deal or considerable impact.

Limitations of this study included the single time point data collection, which prevents assessing the change in burden over time. There are disadvantages common to survey research, such as subject recall bias and that certain response options (e.g., "some impact" vs "considerable impact") may be open to interpretation by the respondents. In addition, respondents who are less comfortable using a computer may be hesitant to participate in an online survey. Another limitation is the small sample size of caregivers participating in this study; particularly the sample size of those caring for patients in stages of CCA other than advanced-stage CCA. Surveying a larger caregiver population, perhaps with more diverse demographics and caring for patients across different stages of CCA, could provide a better understanding of the caregiver burden. However, as the majority of patients with CCA are diagnosed at advanced stages, this may be difficult. Moreover, patients and caregivers experiencing higher burdens may have been more likely to decline participation, so our results may underestimate the burden on both these groups.

A strength of this study was the comprehensive descriptive analysis of the burden of CCA on patients' and caregivers' lives, with respect to living with a CCA diagnosis, treatment and the impact on QoL including sexual function. Moreover, given the evolving treatment landscape of CCA, it is important to have a detailed understanding of the patient and caregiver experience in order to assess and benchmark how their contribution influences clinical care. The voices of patients and caregivers are vitally important when imparting clinical care decisions, as well as in clinical trial design.

Conclusion

In summary, findings from the patient survey emphasize the need for tailored palliative and supportive care interventions for patients with CCA, especially those with advanced disease. The unequivocal positive benefits of early palliative care on QoL for patients with advanced cancer are well-known [46–48]. For example, a randomized control trial [48] evaluating the impact of a palliative care intervention – involving regular educational sessions to encourage patient activation, self-management, and empowerment – showed better QoL scores and improved mean mood score among patients in the intervention group, compared with a 'care-as-usual' control group. The results from the present study support the recommendations of the American Society of Clinical Oncology and World Health Organization that interdisciplinary palliative and supportive care services be made available for patients with cancer and their caregivers [49,50]. Patients need to be made aware of cancer support programs and services. Useful resources include support groups, discussion boards, and educational videos that can be accessed on the American Cancer Society and Cholangiocarcinoma Foundation websites [2,51]. This study also highlights the high caregiver burden and the need for developing resources to better support, educate and connect caregivers. Identification, intervention, education and coordination of services may help to alleviate caregiver burden and improve QoL for both patients and caregivers.

Summary points

- Cholangiocarcinoma (CCA) is a rare and aggressive cancer that typically presents in advanced stages and has a poor prognosis.
- Patients with CCA often have a decreased quality of life (QoL) and require a caregiver due to negatively impacted daily living caused by disease and treatment-related factors.
- This study is the first report to assess the multiple aspects of CCA disease including the impact on daily life, QoL, and mental health in both patients with CCA and caregivers of patients with CCA.
- Results showed fatigue and anxiety were the most common symptoms reported to have a 'considerable' or 'great deal of' impact on the daily life of patients with CCA and patients reported a negative impact of CCA on QoL.
- This study identifies depression as a major psychological challenge for patients with CCA and over one third of patients experienced symptoms consistent with moderately severe or severe depression.
- Over 80% of caregivers reported positive aspects to caregiving including satisfaction that their loved one is well cared for, and that caregiving has taught them to deal with difficult situations.
- The majority of caregivers spent over one third of their time on caregiving duties and reported negative effects including physical impairment and emotional distress.
- This study demonstrates there is a need for tailored palliative and supportive care to be made available for patients with CCA and caregivers of patients with CCA.

Author contributions

All authors contributed to the acquisition, analysis and interpretation of data, as well as to the drafting and critical review of the manuscript, and approved the final version for publication.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

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Ethical conduct of research

The authors state that Western Institutional Review Board reviewed and provided exemption status to this study under 45 CFR §46.104(d)(2). In addition, survey respondents provided permission for their data to be analyzed and published.

Data sharing statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author (email: tajackson@incyte.com).

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