Impact of Early Palliative Care on end of life in Patients with Advanced Biliary Tract Cancer

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Abstract

Background: Most of patient with Biliary Tract Cancer (BTC) has not access to surgery because of Advanced/metastatic disease at diagnosis (aBTC). They receive palliative chemotherapy and/or Palliative Care (PC). We studied if early palliative care referral might influence Overall Survival (OS) and the aggressiveness of end-of-life care.

Participants: We conducted a retrospective multicentric cohort study in patients with non-curative BTC, diagnosed between 2013 and 2019 in 6 hospitals of Eastern France. PC was defined a specialist-delivered palliative care encounter.

Results: 200 patients with aBTC were included. 87 (44%) never received PC, 30 (15%) had very early PC (<3 months after aBTC diagnosis), 20 (10%) had an early PC (3-6 months), and 63 (32%) had late PC (>6 months). The median time between referral and death was 0.9 to 1.3 months. OS were 12.4 months (no PC), 3.0 months (PC<3 m), 6.4 months (PC 3-6 m), 16 months (PC>6 m). There was no evidence for survival improvement with early PC. PC tended to reduce chemotherapy near death (37% without PC, 30% with PC<3m, 11% with PC 3-6m, 10% with PC>6m), visits in emergency department (ED) during final month (respectively: 36%, 20 %, 15%, and 7%), intensive care unit hospitalizations (ICU) near death (13%, 0%, 0%, 2%). Place of death seemed to be positively impacted by PC (conventional acute unit, respectively: 73%, 21%, 21%, 25% and ICU or ED: 8%, 0%, 5%, 2%).

Conclusion: Referral to PC remains too late in the support of patients with aBTC. Our practice should evolve: all patients with aBTC should be referred to early PC in palliative care unit after diagnosis to improve the management of end-of-life, symptoms, and family needs.

Keywords: Cholangiocarcinoma • Biliary tract cancer • Gallbladder carcinoma • Palliative care • survival

Abbreviations: BTC: Biliary Tract Cancer; aBTC: advanced Biliary Tract Cancer; CCA: Cholangiocarcinoma; iCCA: intra Hepatic Cholangiocarcinoma; eCCA: extra Hepatic Cholangiocarcinoma; pCCA: peri Hilar Cholangiocarcinoma; ED: Emergency Department; ICU: Intensive Care Unit; OS: Overall Survival; PCU: Palliative Care Unit; PCT: Palliative Care Teams; PCR: Palliative Care Referral; PS: Performans Status

Introduction

Biliary Tract Cancers (BTC) is rare primary liver cancers but its incidence is increasing. Prognosis remains poor with Overall Survival (OS) reaching 6 to 11 months [1,2]. That poor prognosis is attributed to challenges in early detection (due to delayed symptoms), low opportunity for radical resection and limited response to chemotherapy and/or radiotherapy. Indeed, only 20% to 30% of patients diagnosed with BTC have access to surgery, which is the only curative-intent treatment [3]. Therefore, most of patients receive palliative systemic therapy (chemotherapy, targeted therapy, and immunotherapy) or exclusive supportive care.

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Palliative Care Teams (PCT) is composed of several actors making possible a multidisciplinary and global comprehensive care: physical, emotional, social (family caregivers…), spiritual (meaning, dignity, faith…), informational (prognosis, illness understanding…) [4]. Palliative care (PC) and systemic palliative therapy are complementary approaches that should be associated early for more benefits. In 2017, the American Society of Clinical Oncology (ASCO) published recommendations about palliative care, specifying that palliative care should be introduce early in cancer management, at diagnosis and with the beginning of systemic therapy [5].

Despite these recommendations, and probably due to a lack of palliative care teams, patients' referral to PCT in daily practice is often late (eg: no more therapeutic options, general condition too weak).

Recent studies demonstrated the positive impact of PC on aggressiveness of end-of-life care that includes chemotherapy, intensive care unit admission, Emergency Department (ED) visit and acute unit hospitalization, during last month of life [6]. In pancreatic cancer in a retrospective study the positive impact of a PC consultation on these above mentioned end-of-life indicators [7]. These results were confirmed in a prospective multicentric randomized controlled Italian trial including 206 patients with metastatic pancreatic cancer [8].

Recently, the concept of PC has evolved with the issue of the timing of palliative care referral (PCR), and the benefits of an early palliative care. An

Australian retrospective study highlighted the use of early PC to improve aggressiveness of end-of-life care, compared to late PC (>90 days before death) in patients with pancreatic cancer [9].

Moreover, a retrospective study among patients in advanced lung cancer shown that early PC (30 to 365 after diagnosis) was significantly associated with an increase of OS (aHR, 0.47; 95% CI, 0.45-0.49). In 2021, a randomized study of advanced esophagogastric cancer also demonstrated an OS improvement in case of early interdisciplinary supportive care.

In the context of aBTC, which prognosis is poor with frequent uncomfortable symptoms as jaundice, anorexia, asthenia, abdominal pain, weight loss, psychological suffering; palliative care team have a crucial role to provide a multidisciplinary take of care. To our knowledge, no study assessed early PCR in aBTC patients. We conducted a retrospective multicentric study to assess the relationship between early PCR and survival (primary outcome) and to explore the impact of early PCR on treatment aggressiveness near the end of life [10-12].

Materials and Methods

We conducted a retrospective multicentric study including patients with a diagnosis of aBTC (cholangiocarcinoma and gallbladder) between January 1, 2013 and December 31, 2019. We included patients of 6 University hospitals of Eastern France (Nancy University Hospital, Besançon University Hospital, Dijon University Hospital, Reims University Hospital, Strasbourg University Hospital, and Strasbourg ICANS Centre for the Treatment of Cancer). Follow-up data were available until January 2021. Detailed clinical and pathology data were collected for all patients through a custom-made questionnaire providing epidemiological informations, data about aBTC (age at diagnosis, risk factors, treatment) and palliative care support (time to BSC referral, end-of-life acute events and condition). When necessary, we consulted medical files on site. Ethics approval was obtained from the Ethics Committee of Nancy CHU September 8, 2020, Licence number 272. Patients received an information letter and had 30 days to ask their withdrawal from the study. After this delay, they were considered as participants.

Cohort selection

Patients were eligible if they were ≥ 18 years old, had and histologically confirmed, locally advanced or metastatic cholangiocarcinoma or gallbladder adenocarcinoma diagnosed between January 1, 2013 and December 31, 2019. Patients were included regardless their Eastern Cooperative Oncology Group (ECOG) performance status

Patients were excluded if they died within a week after diagnosis and if insufficient clinical data were available.

Exposure

PC was defined as a specialist-delivered palliative care encounter received inpatient or outpatient setting after aBTC diagnosis. It could be with a mobile PCT, in hospitalization (palliative care units, PCU) or in consultation. Data were collected in electronic medical records (DxCare software).

Study objectives

Primary outcome was OS after aBTC diagnosis according to PCR. We secondary evaluated the impact of early PCR on the aggressiveness of end-of-life care, which included place of death (at home with home hospitalization, at home without home hospitalization, intensive care unit, conventional acute unit, palliative care unit), last-month chemotherapy, last-month ED visit and last-month intensive care unit hospitalization. Continuous variables were summarized by descriptive statistics (number of cases, mean, median, and quartile) and categorical variables were summarized with percentages. We also compared the most frequently reported reasons to referral and proposals made by PCT.

Statistical analysis

Characteristics of sample were described by percentage for categorical variables and median with inter-quartile range (Q1-Q3) for continued variables. OS was calculated from the date of diagnosis of advanced BTC until the date of death or date of last follow-up and Kaplan-Meier curve was realized for each group. A second analysis was made by calculating the time from the date of first meeting with PC until the date of death or date of last follow-up. To address potential selection bias, we have planned to make a propensity score of receiving palliative care, composed of metastatic stage, age (>75 years old), performans status OMS, Charlson score (>3). This approach minimized selection bias by comparing patients with a similar likelihood of receiving PC. Due to heterogeneity between study groups, propensity score has not been achieved. Clinical characteristics among these four groups were too different to produce a reliable comparison. The significant threshold was fixed at 5%. All analyses were performed with SAS® software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics

Two hundred patients with aBTC were included in our study. Median age at aBTC diagnosis was 67.6 years old (20-91 years old). 61% of the patients were men. Most of the tumours were intrahepatic cholangiocarcinoma (iCCA) (51%), then perihilar (pCCA) (24%), gallbladder (18%) and distal CCA (7%). 62.5% patients had distant metastasis at diagnosis and 37.5% were locally advanced. About well-known BTC risk factors, 27% of patients were smokers and 18% had a heavy alcohol consumption, 19% were obese (body mass index ≥ 30 kg/m^2), 31% had type II diabetes, 14% had a cirrhosis. Only 2 patients had a primary sclerosing cholangitis. The most common symptoms at diagnosis were abdominal pain (40%), jaundice (33%), asthenia (31%) and anorexia (28%). A quarter (26%) had a prior curative-intent treatment before their relapse (surgery or locoregional treatment) and then a non-curative recurrence. Systemic palliative chemotherapy was prescribed for 82.5% of the patients, and 17.5% received exclusive supportive care (Table 1).

Table 1. Sociodemographic and clinical data of frail patients with cancer and breakthrough pain.

Variable	Total (n=200)
Age, years (median, IQR)	67.6 (60.7 – 74.4)
Gender, n (%)	
Male	123 (61.5%)
Female	77 (38.5%)
Performance status, n (%)	
0-1	152 (77.2%)
2	29 (14.7%)
3-4	16 (8.1%)
missing	3
Denutrition (IMC <18.5 or <21 for patients older than 70 years)	7 (3.7%)
Risk factors of biliary tract cancer	
Obesity (IMC >30), n (%%)	36 (18.8%)
Diabetes, n (%)	62 (31.0%)
Smoker, n (%)	53 (26.5%)
Chronic alcoholism, n (%)	36 (18.0%)
Cirrhosis, n (%)	28 (14.0 %)
Primary sclerosing cholangitis, n (%)	2 (1.0%)
Diagnosis	
Primary tumor site, n (%)	
Intrahepatic	101 (50.8%)
Perihilar (=Klatskin)	48 (24.1%)
Gallblader	35 (17.6%)

Distal	14 (7.0%)
Hepatocholangiocarcinoma	1 (0.5%)
Missing	1
Disease status, n (%)	
Locally advanced	75 (37.5%)
Metastatic	125 (62.5%)
Symptoms at diagnosis (4 most common symptoms for 197 patients with available data)	
Abdominal pain	79 (40.1%)
Jaundice	65 (33.0%)
Asthenia	61 (31.0%)
Anorexia	56 (28.4%)
Absence of symptoms	47 (23.9%)
Albumine median (g/L) (N=175, IQR)	34 (29 – 39)
CA 19-9 median (N=153, IQR) (kUI/L)	263 (27 – 1954)
Treatment	
Prior curative-intent treatment, n (%)	52 (26.0%)
Chemotherapy received, n (%)	
Yes	165 (82.5%)
No	35 (17.5%)
Type of L1 chemotherapy regimen, n (%)	N=165 (82.5%)
Among 165 patients who received L1 chemotherapy (N=165)	
Gemox	110 (66.7%)
Gemcis	23 (13.9%)
Gemcitabine	16 (9.7%)
Others or unknow	16 (9.7%)
Patients treated with L2 chemotherapy, n (%)	N= 93/165 (56.4%)
Folfiri	42/93 (45.2%)
Lv5fu2 cisplatine	22/93 (23.7%)
Folfox	8/93 (8.6%)
Others or unknow	21 (22.6%)
Patients treated with L3 chemotherapy, n (%)	N= 40/165 (24.2%)
Patients treated with L4 chemotherapy, n (%)	13/165 (7.9%)
Palliative care	
No encounter with palliative care	87 (43.5%)
Palliative care	113 (56.5%)
Home hospitalization	
Yes	39 (19.6%)
No	160 (80.4%)
Unknown	1

Among the 165 patients who received chemotherapy, the most frequent (67%) first-line regimen was Gemcitabine+Oxaliplatine (GEMOX). Other protocols administred as first line palliative therapy where Gemcitabine+Cisplatin (14%) and gemcitabine alone (10%). More than half of the patients received a second-line chemotherapy (56%), mainly 5FU-based regimen (54% received FOLFIRI).

Palliative care

Most of included patients (56%) met the PCT at least once (Table 1). The PCT were constituted of at least one specialized doctor and a nurse. The mean time to first PCR was more than 6 months after diagnosis (9.7 months) (Table 2).

Table 2. Characteristics of breakthrough pain in frail patients with cancer.

Variable	N=113 (palliative care)
Mean time of first PC encounter after diagnosis (months)	9.7
Timing of the encounter after diagnosis	
< 3 months after diagnosis	30 (26.5%)
3-6 months after diagnosis	20 (17.7%)
>6 months after diagnosis	63 (55.7%)
Type of first encounter	
Mobile palliative care teams	74 (65.5%)
Palliative care units/beds or hospital day care	29 (25.7%)
Consultation	10 (8.8%)
Encounter during the last hospitalization (before death)	13 (11.5%)
Most frequently reasons for referral among 111 patients with available date	
Asthenia	64 (57.7%)
Decision for becoming and place of care	46 (41.4%)
Pain	45 (40.5%)
Psychological symptoms	13 (11.7%)
Following the cessation of active therapeutics	19/92 (10.9%)
Most frequently treatment/take of care by the PC team among 106 patients with available data	
Decision for becoming and place of care	57 (53.9%)
Opioids (start or dose increase)	52 (48.6%)
Anxiolytics	38 (35.8%)
Mouth care	38 (35.8%)

In most of the 6 centres, patients benefit of supportive care through an encounter with mobile PCT (65%), less through a hospitalization in PC units (26%) or a consultation (9%). In one of the centres (ICANS), we notice there was hospital day care that allows a global take of care, with participation of several stakeholders during one day.

This support by PCT mainly often results of a request by the oncologist. The most frequent reasons for referral were asthenia (58%), decision for place of care (41%) and pain (40%). PCR interventions were "decision for becoming and place of care" (54%), opioids treatment (49%), anxiolytics (36%), mouth care (36%) (Not mutually exclusive).

Impact of palliative care on overall survival

Among the 200 included patients, 188 (94%) died at the end of data collection. 87 (43.5%) did not received PC, 30 (15%) had early PC (<3 months after diagnosis), 20 (10%) had PC 3 to 6 months after diagnosis, and 63 (31.5%) had late PC (> 6 months). Median OS were respectively in the four groups 12.4 months (no PC), 3.0 months (PC < 3 months), 6.4 months (PC 3-6 months) and 16.0 months (PC >6 months) (Table 3).

Figure 1 represents OS with or without PC. OS was not significantly different between PC and no PC groups (p=0.34). Figure 2 represents survival according to the first PCR. No significant difference was observed between groups (p=0.79). Time between PCT contact and death were 0.9 months (PC < 3months), 1 month (PC 3-6 months) and 1.3 months (PC >6 months) (Figures 1 and 2).

Table 3. Drugs administered to frail patients with cancer and breakthrough pain for the treatment of chronic pa Impact of palliative care on survival and aggressiveness of end-of-life care: Comparison between the 4 groups (No PC, PC<3months after aBTC diagnosis, PC 3-6 months after aBTC diagnosis, PC>6 months after aBTC diagnosis).

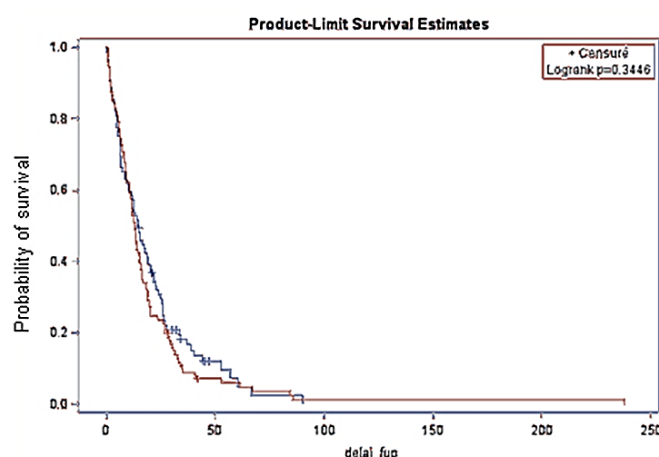| Variable	No PC N=87 (43.5%)	PC <3months N=30 (15.0%)	PC 3-6months N=20 (10.0%)	PC >6months N=63 (31.5%)	All PC N=113(56.7%)
Description of the groups					
Age ≥ 75 years old	22	7	6	12	25
Performans status ≥ 2	19	18	3	5	26
Unknow		1	1	1	3
Charlson ≥ 2	31 (35.6%)	14 (46.7%)	9 (45.0%)	20 (31.7%)	43(-38%)
Metastasis	56	19	14	38	71
Unknow	1				
Chemotherapy received	73	12	19	61	92
Death	78	30	20	60	110 (97.3%)
Survival (N=188 patients dead)					
Overall survival in months (median)	12.4	3	6.4	16	-
Delay between PC contact and death in months (median)	-	0.9	1	1.3	-
Comparison of end-of-life care (N=188 patients dead)					
Place of death	N=188	No PC N=78	PC <3m N=30	PC 3-6m N=20	PC >6m N=60	All PC N=110
Home	26 (13.8%)	7 (9.6%)	4 (13.8%)	2 (10.5%)	13 (22.0%)	19(17.3%)
Home hospitalization	12 (6.4%)	7 (9.6%)	1 (3.4%)	0	4 (6.8%)	5(4.5%)
Conventional acute unit	78(41.5%)	53 (72.6%)	6 (20.7%)	4 (21.1%)	15 (25.4%)	25(22.7%)
Palliative care unit	56 (29.8%)	-	18 (62.1%)	12 (63.2%)	26 (44.1%)	56(50.9%)
Intensive care unit or emergency department	8 (4.3%)	6 (8.2%)	0 (0%)	1 (5.3%)	1 (1.7%)	2(1.8%)
Unknow	8	5	1	1	1	3
Cause of death (3 most frequents)					
Deterioriation of general condition	39 (59.1%)	27 (93.1%)	17 (89.5%)	50 (92.6%)	94(85.4%)	
Sepsis	16 (24.2%)	2 (6.9%)	0 (0%)	1 (1.9%)	3(2.7%)	
Gastro intestinal bleeding	3 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0%	
Unknow	12	1	1	6	8	
Chemotherapy near death (last month) (among the 157 dead patients who received chemotherapy)	23/63(36.5%)	3/12(30.0%)	2/19(10.5%)	6/58(10.3%)	11/89(12.4%)	
Unknow	1	2	-	-	2	
Emergency department visit near death (last month)	27 (35.5%)	6 (20.0%)	3 (15.0%)	4 (6.8%)	13 (11.8%)	
Unknow	2	-	-	1	1	
Intensive care unit hospitalization near death (last month) Unkown	10 (12.8%)	0 (0%)	0 (0%)	1 (1.7%)	1 (0.9%)	
Unknow	2	-	-	1	1	

Figure 1. Association between survival and palliative care: Palliative care *vs.* no palliative care.
Note: + Censure, Logrankp=0.7953, (———) Meeting with palliative care team, (———) Without meeting with PCT

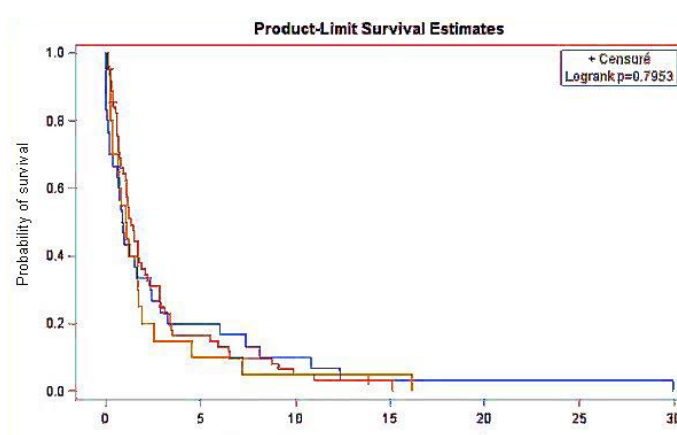**Figure 2.** Survival after first meeting with palliative care team.
Note: + Censure, Logrankp=0.7953, (———) SP<3months, (———) SP<3-6months, (———) SP>6months

Impact of palliative care on aggressiveness in end-of-life care

Place of Death: Place of death seemed to be influenced by PC (not significant), especially when PCR was early (<3 months after diagnosis). PC was associated with less death in conventional acute unit, intensive care unit and ED (respectively 72% no PC *vs.* 21% early PC and 8% no PC *vs.* 0% early PC) and more death in palliative care unit (Table 3).

Last-month Chemotherapy: PC was associated with less chemotherapy during last month of life (non-significant): 36% (no PC), 30% (PC <3months), 10% (PC 3-6months), 10% (PC >6months).

Last-Month Emergency Department Visit: Results were similar for ED visits near death. PC was associated with less visits in ED, However the support of early PCR was not significant (20% PC<3months, 15% PC 3-6months, 7% PC >6months; versus 35% no PC).

Last-Month Intensive Care Unit Hospitalization: Hospitalizations in intensive care unit seemed to be impacted by PC: 10 patients in the no PC group were admitted in ICU versus 1 patient in the PC group.

Discussion

Because of its advanced/metastatic stage at diagnosis and its poor prognosis, the management of aBTC should be inseparable from the initiation of early palliative care, as soon as systemic palliative therapy is initiated.

To our knowledge, the present study is the first which provides real-world data about PC settings and which assess the impact of this support on survival in patients with aBTC.

Indeed, there is scarce literature available about biliary tract cancer and PC. Therefore, we will compare our data with available literature regarding advanced/metastatic pancreatic ductal adenocarcinoma, which prognosis is similar.

In our study, 17% of patients were not able to received systemic treatment, which is different from other published studies which included 3650 iCCA patients). Such a difference might be partly explained, by the fact that in this above mentioned study, all patients with advanced or metastatic BTC were included, even those without accessible histological evidence, making it feared that their general condition was too poor at diagnosis to obtain histological evidence. In the same way, more than a half (56%) of chemotherapy-treated patients had a second-line chemotherapy, which is more than other studies (less than one third) [13,14].

Our main objective was to assess if early PC could improve OS. We found no evidence that OS was better in PC group in comparison to no PC group. It could be explained by the heterogeneity between groups. Indeed, groups were not comparable: patients who were referred earlier to PCT had more comorbidities and more advanced BTC. The group of patients who met PCT early after aBTC diagnosis had the worst survival due to several poor prognosis factors: high performans status (≥ 2 for 62% of them), more comorbidities (Charlson Index Score ≥2 for 47% of them), and only one third of them was able to receive palliative chemotherapy. Consequently,

causes of death seem to be also different between groups. Because patients from early PC groups had more frailties and comorbidities, related-cause of death were mainly due to deterioration of general conditions (93% for early PC *vs.* 59% no PC). Differences in the rate of acute events were also noticed, as sepsis (7% early PC *vs.* 24% no PC) or gastro-intestinal bleeding (0% early PC *vs.* 4% no PC). On the contrary, patients who never receive PC died more from acute complication as sepsis or bleeding, with more hospitalizations in intensive care unit.

Differences are also due to the retrospective character of our study, which reflects our daily clinical practice, with patients referred to PCT 0.9 to 1.3 months before death, usually when systemic treatments are no more possible. The early PC group is representative of these practices: patients who were referred early to PCT after aBTC diagnosis had symptomatic advanced or metastatic BTC cancer and presented altered general conditions. This is probably the main explanation for poor OS (3 months) in that group. In such situations, PCT cannot build strong relationship with patient and their family. However, important times for exchanges should be established, as interruption of systemic chemotherapy, end-of-life preferences, and meeting family members to have a global action. These results are similar to a French study published in 2017, about all patients addressed to PCT of 25 Parisians hospitals: Median survival time after first PCT meeting was 31 days, and 18% of the patients first met PCT 3 days before death [15].

In 2017, the American Society of Clinical Oncology (ASCO), published recommendations about palliative care, and especially mentioned that patients with advanced cancer should receive dedicated palliative care services early in the disease course and concurrent with active treatment. In our study, 56% of the patients have met at less once the PCT, which is similar that a retrospective study in pancreatic cancer patients (52%). However, time-to-referral seems too late for impacting prognosis. Average time between diagnosis and PCR was 9.7 months, although median OS fluctuates from 3 to 16 months. Among 11% of the patients who met PCT, this meeting happened during the last hospitalization (a few days before death), which is too late.

The most common reasons for PCR in our study were asthenia (58%), "decision for becoming and place of care" (41%), pain (40%), psychological symptoms (12%) and then following the cessation of active therapeutics (11%). As a comparison demonstrated in their study that the 3 major reasons for PCR (for all cancer types) were pain (57%), early encounter (24%), decision for place of care (18%) and then in 6th position "decision to withhold or withdraw treatments" (9.3%). In our study, patients were mostly referred to PCT for difficulties for end-of-life management. Late PCR does not allow PCT to be a part of the decision about active treatment, which should be discussed in a multidisciplinary team.

In our study, meeting PCT is associated with an impact on place of death (Table 3). When they received early PC, fewer patients died in conventional, emergency or intensive departments. In a retrospective study published in 2015, conducted in more than 500 000 patients with advanced cancer, proportion of death in PC units was 10% showed that this proportion reached 30% when patients were referred to PCT. It reflects the positive impact of PC on the place of death, with fewer deaths in acute care units. Death in appropriate and dedicated department is important for a better management of end-of-life. In palliative care units or home hospitalization, PCT are familiar with those situations, and are able to anticipate future needs for patients, and to discuss of their preferences in order to head off difficult situations of end-of-life. In a retrospective study performed in patients with pancreatic adenocarcinoma, chemotherapy was prescribed during last month in 17% in case of early PCR and 25% in case of late PCR (not significant, p=0,22). In our study, 18% of patients received palliative chemotherapy within the last month of life (36% no PC, 10%-30% with PC), which is similar to previous studies. PC seems to reduce end-life chemotherapy. Chemotherapy at end-of-life does not bring any benefits for patients, leading to a worsening of the side effects of systemic drugs (eg: asthenia, nausea, infections leading to hospitalizations). Such situations could be avoided with early PCT meeting [16].

In the Australian study focusing on advanced/metastatic pancreatic cancer patients early PC allows a significant reduction of last-month visit in ED (24%) in comparison to late PSC (42%) (p=0,003). In our study, in the PC group, ED visit proportions varied from 7% to 20%, compared with 35% in the no PC group. Our data also suggests that PC reduces ED visits during the last month of life.

In 2005, Earl et al. proposed some objectives to evaluate aggressiveness in end-of-life care

1. Less than 10% of patients should receive chemotherapy in the last 14 days of life. In our study we collected last-month chemotherapy rate (36% without PC *vs.* 10% to 30% with PC)

2. Less than 4% of emergency room visits. In our study we had 35% no PC group and 7% to 20% PC group

3. Less than 17% death in an acute care hospital. We had 8% death in ICU in non-PC group *vs.* 0% to 5% in PC group. In conventional acute unit we had 73% in non PC group *vs.* 21% to 25% in PC group.

4. Less than 4% of admission in ICU. In our study this objective is achieved for the PC group (0%-2%) but no for the no PC group (13%).

One major limitation of our study is its retrospective character leading to heterogeneity into groups and therefore a bias especially for overall survival in the four groups.

Another important limitation of our study is the differences of accessibility and support by the PCT. Indeed, although recommendations are established, referral to PCT is not standardized in France. Human and financial resources allocated to palliative care are different in France and vary from one center to another. This is well illustrated in our work by the presence of a day hospital dedicated to palliative care in only one of the 6 centers studied (Strasbourg, ICANS).

This study provides important data about end-of-life management, and partnerships with PCT for patients suffering from aBTC. Although no evidence for improvement of OS with early PCR was demonstrated, PC is introduced too late in the patient's care pathways to improve prognosis. However, PC have a positive impact on end-of-life with limitation of futile systemic chemotherapy, fewer visit in ED, fewer hospitalization in ICU, and fewer death in a conventional acute unit or ICU.

Conclusion

This study provides important data about end-of-life management, and partnerships with PCT for patients suffering from aBTC. Although no evidence for improvement of OS with early PCR was demonstrated, PC is introduced too late in the patient's care pathways to improve prognosis. However, PC have a positive impact on end-of-life with limitation of futile systemic chemotherapy, fewer visit in ED, fewer hospitalization in ICU, and fewer death in a conventional acute unit or ICU.

Despite ASCO recommendations of 2017 in favour of early PCR in cancer course (concomitant to active therapy), we observed that patients are mainly referred to PCT at end-of-life clinical in daily practise. Efforts should be done for a better education and access about PCR role in a multidisciplinary approach in cancer. Introduction of early PC should endorse a central role in aBTC cancer, with many positive consequences on end-of-life preferences, discontinuation of useless chemotherapy, better management of symptoms and family needs. PC should also evolve for each patient according to disease, prognosis, comorbidities, and symptoms, moving towards a "personalized early PC".

Declarations

Ethics approval and consent to participate

Consent for publication

Not applicable for patients.

Availability of data and material

Conflicts of interest

The authors declare that they have no competing interests (files attached)

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Author's contributions

Supervision, concept and design: A. Lopez. Data acquisition: M. Miralles, C. Borg, S. Manfredi, A. Minello, O. Bouché, M. Tambou, D. Mutter, P. Chiappa, J-E. Kurtz, A. Lopez. Statistical analysis: A. Luc, C. Baumann. Manuscript writing and editing: M. Miralles, M. Muller, C Borg, S. Manfredi, A. Minello, O. Bouché, M. Tambou, D. Mutter, P. Chiappa, J-E. Kurtz, A Luc, C. Baumann, A. Lopez. Drafting of the manuscript: A. Lopez, M. Miralles, and M Muller. Final approval of manuscript for all authors.

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Consent to participate

Permission to publish the case anonymously was obtained from patients.

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