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Effects of Implementation of a National Fast Track Clinical Pathway for Hepatocellular Carcinoma in Western Denmark

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ABSTRACT

Background & Aims: In 2009, the Danish Government instituted "Fast Track Clinical Pathways" (FTCP) to accelerate diagnosis and treatment of cancers including hepatocellular carcinoma (HCC). We examined how the implementation of FTCP affected the time from referral to diagnosis and treatment as well as the patient survival.

Methods: 309 consecutive patients with suspected HCC were included, 79 referred during the period 2007-2008 (before FTCP) and 230 during 2009-2011. Of those, 271 (88%) were diagnosed with HCC and 161 (60%) had cirrhosis, in most cases caused by alcohol.

Results: The time from referral to the first visit was reduced from a mean 16.4 (11.5) to 5.4 (6) days ($p<0.001$) and the time from the first visit to the Multidisciplinary Tumour Conference (MDT) treatment decision from 34.9 (27.9) to 16.1 (14.4) days ($p<0.001$). The total time from referral to treatment was reduced from 53.2 (37.9) to 35.9 (23.1) days ($p<0.001$). There was a weak trend of improved survival after FTCP: 231 (147-368) vs. 293 (227-396) days ($p=0.11$).

Conclusions: The implementation of FTCP reduced the total time from referral to treatment by three weeks; however, without significant effects on overall mortality. While shortened waiting time is a comfort for the patient, it remains to be elucidated whether it will change the prognosis.

Key words: hepatocellular carcinoma – fast track clinical pathway – survival.

Abbreviations: FTCP: Fast Track Clinical Pathway; HCC: hepatocellular carcinoma; MDT: multidisciplinary tumour conference; RFA: radiofrequency ablation; CT: computed tomography; MRI: magnetic resonance imaging; MELD: Model for End-Stage Liver Disease; WHO: World Health Organisation; SD: Standard deviation.

INTRODUCTION

For decades, Danish cancer patients have had poorer survival compared to cancer patients in the other Nordic countries [1]. Therefore, the Danish Government recommended cancer to be considered as an acute clinical condition and The Danish National Board of Health developed a national cancer plan, which was implemented in the Danish healthcare system by January 1st 2009 [2]. The focus of this political decision was to develop integrated "Fast Track Clinical Pathway" (FTCP) as organizational and clinical standards for the diagnosis and treatment for all cancer types.

The FTCP for hepatocellular carcinoma (HCC) was developed by national HCC specialists [3] to reduce time from referral to treatment with the overall aim to improve survival. In addition, all HCC patients would be treated by highly specialized and centralized multidisciplinary teams as outlined by international clinical guidelines [4].

The incidence and prevalence of HCC is globally heterogeneous with the highest rates in Southeast Asia [5]. In Denmark, HCC is rare, with an incidence rate of approximately 4.6 per 100.000 per year [6, 7]. Hepatocellular carcinoma usually develops in the setting of liver cirrhosis and its prognosis is dismal with a 5-year survival of 10-15% [8, 9]. Treatment options for HCC depend on the tumour burden (size and stage, uni- or multifocality, vascular invasion and extrahepatic disease), the underlying liver function and the performance status [10]. The curative options are

surgical resection, radiofrequency ablation (RFA) or liver transplantation. However, at the time of diagnosis many patients are not candidates for curative treatment because of poor liver function, multifocal disease or advanced cancer with extrahepatic disease [11]. It is therefore important to diagnose patients early when curative treatment is possible. Delayed diagnosis due to waiting time and other organizational delays may influence survival; these delays can be minimized by improving logistics and patient flow, e.g. FTCP.

We hypothesized that the FTCP would improve the time from referral to diagnosis and treatment providing an effect on overall mortality. We aimed to investigate this in HCC patients evaluated at a Danish tertiary liver cancer centre before and after implementation of FTCP.

METHODS

Description of FTCP

The criteria for HCC patients to enter the FTCP are: a possibly malignant solid mass in the liver detected by any imaging technique (not focal nodular hyperplasia or haemangioma) and at least one of the following: 1) increasing levels of alpha-fetoprotein; 2) cirrhosis of any etiology; 3) hemochromatosis or 4) chronic hepatitis B or C as defined in the Danish FTCP HCC guideline [3].

If the patient is admitted to the FTCP, the "journey of the patient" starts within 48 hours.

Time limits

The Danish National Board of Health states time limits for all steps in the clinical pathway [3]: from referral to first consultation, 6 calendar days; from the first consultation to confirmation of the diagnosis and clinical treatment decision, 31 calendar days; and 10-15 calendar days from the day of clinical treatment decision to treatment (Fig. 1). The total time limit for all steps in the clinical pathway is 47 calendar days.

Time frame of pathway elements

To adhere to these time limits, the FTCP is organized as follows: day 0: the patient is referred to the coordinating nurse who books an appointment and informs the patient. In the outpatient clinic and department of radiology open slots secure patient visits and CT/MRI imaging. On day 2-6 the first consultation, and from day 2 to 31 further investigations can be scheduled e.g. other imaging modalities, liver biopsy, pathology report, the multidisciplinary tumour board (MDT) meeting etc. Not later than day 31 the patient will be evaluated at the MDT and immediately be informed about the results, diagnosis, decision of treatment or the need for any supplementary examinations. The waiting time may only be prolonged if it is clinically justified, such as the need of supplemental imaging or further immunohistochemical staining of a biopsy. All the decisions regarding HCC patients are taken at bi-weekly MDT conferences with the participation of hepatologists, liver surgeons, interventional radiologists, oncologists and specialists in nuclear medicine. Before the introduction of FTCP, there was no time frame for pathway elements, nor a dedicated coordinating nurse, and the handling of patients was at the clinician's discretion. Therefore, patients often had an unjustified delay in referral, which was one of the reasons to implement FTCP.

Patients

We performed a before-and-after historical cohort study of all patients referred to our tertiary centre with a catchment population of 2.5 million in Western Denmark for a specialized multidisciplinary evaluation of diagnosis and treatment options for HCC.

We included all patients (n=309) referred with suspected or confirmed HCC during the 5-year period from January 1st 2007 to December 31st 2011, 79 before the FTCP and 230 after. The referral pattern changed from the first period to the second. Before 2009 the referral of patients was mostly from the Region of Mid-Jutland, but from January 1st 2009 patients were also referred from the Region of North-Jutland and the Region of Southern Denmark. Seventy-six patients from the early cohort had confirmed HCC, and 195 in the late cohort. The FTCP was effective as of January 1st 2009. Data were collected at the first visit using a structured clinical report form and retrospectively retrieved and supplemented from patient files. There were no major differences in treatment policies between the two periods.

From patients' medical records, we retrospectively retrieved information regarding age, gender, year of admission, origin of the patients' referral, date of entry into the FTCP, the first hospital visit, MDT, clinical decision, and beginning

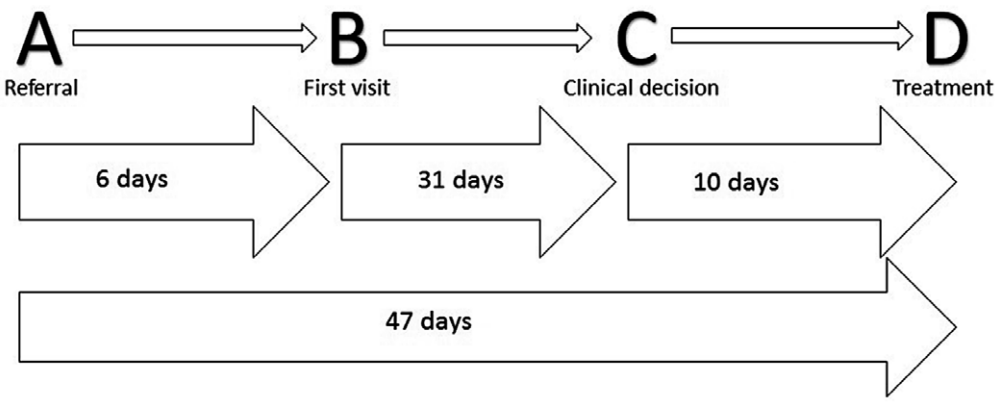

Fig. 1. The FTCP for HCC patients with time intervals as instituted by the Danish National Board of Health.

of treatment. In addition, we recorded underlying liver disease, type of tumor (solitary, diffuse, multifocal) and liver function tests (alanine aminotransferase, bilirubin, albumin, creatinine, C-reactive protein, leucocytes, neutrophils, hemoglobin, thrombocytes, partial prothrombin time and alpha-fetoprotein). The liver disease status was assessed by the presence of ascites and encephalopathy; the Child-Pugh and MELD scores were recorded for the patients with cirrhosis. In addition, WHO Performance Status was recorded. In patients with cirrhosis, the HCC diagnosis was based on tri-phasic CT or MRI scans with the presence of a hypervascular tumour with wash-out in the portal phase according to international guidelines [4]. Liver biopsy was performed when CT/MRI demonstrated an uncharacteristic tumour in a cirrhotic patient and in any non-cirrhotic patient.

Data analysis

Data were analysed by the statistical package Stata 11.1. Continuous variables are presented as median and range or mean and standard deviation (SD) for normally and non-normally distributed data, respectively. Categorical variables are given as absolute numbers and percentages. Differences between the groups were evaluated by the Mann-Whitney test or X^2-test when appropriate. A p-value <0.05 was considered statistically significant.

Time intervals were compared between groups by log-rank test and reported as mean and SD.

We compared overall survival between groups using Kaplan-Meier plot and log rank test. Results were reported as percentage survival with 95% confidence interval. The survival was adjusted for age, gender, MELD and TNM status and palliative status using Cox regression model and reported as hazard ratio. The effect of age was visualized using splines which did not suggest including age as a non-linear effect. The assumption of proportional hazards was inspected using log-log plots. Further model validation was performed by evaluating the Cox-Snell residuals and that did not reject the model.

RESULTS

During the 5-year period, 309 patients with suspected or confirmed HCC were referred (Table I). Of the 309 patients 271 (88%) were diagnosed with HCC, 161 (60%) of these had cirrhosis in the majority caused by alcohol. The patients without a HCC diagnosis had other cancer diagnoses or a benign tumour and were excluded from further analysis. There was no significant difference between the HCC patients in the two time periods regarding their liver and renal function, Child-Pugh and MELD score, WHO performance status and TNM classification (Table I).

The mean time from patient referral to end of initial diagnostic work-up decreased from 16.4 days to 5.4 days following FTCP implementation (p<0.001) (Table II). Before FTCP, 24% of patients had a first visit within 6 days, which increased to 70% in the later period. The interval from first visit to clinical decision did not change significantly.

The interval from referral to clinical decision decreased from 34.9 days to 16.1 days (p<0.001) (Table II). Thus, 54% of the patients in the first period had a diagnosis and treatment decision within 31 days, while the percentage increased to 86% in the late period. However, the interval from clinical decision to treatment did not change (20.7 days, Table II). The total time from referral to treatment was reduced from 53.2 days to 35.9 days (p<0.001).

The patients' overall survival time increased slightly after FTCP: 231 (CI 227-396) days vs. 293 (CI: 227-396) days, but did not reach statistical significance (p=0.11) (Fig. 2). Also 1- and 3-year mortality rates did not differ before and after FTCP

Table I. Clinical and biochemical characteristics of the 271 patients diagnosed with HCC in the two time periods.

	2007-2008 (n=76)	2009-2011 (n=195)	p-value
Cirrhosis, n (%)	45 (60)	116 (60)	0.55
Underlying liver diease, n(%)			
Alcohol	15 (19.7)	64 (32.8)	
Hepatitis B or C	15 (19.7)	28 (14.4)	
Cryptogenic	9 (11.8)	21 (10.8)	
Autoimmune	5 (6.6)	3 (1.5)	
NASH	2 (2.6)	3 (1.5)	
Haemochromatosis	2 (2.6)	7 (3.6)	
Gender male (%)	60 (78,9)	156 (79,6)	0.91
Age	65 (25-85)	67 (17-86)	0.12
Bilirubin (μmol/L)	19 (4-444)	15 (3-367)	0.03
Alfafetoprotein (g/L)	79 (0-644502)	111 (2-406900)	0.66
Albumin (mg/L)	35 (18-46)	35 (16-49)	0.73
Creatinin (μmol/L)	71 (42-702)	74 (37-360)	0.44
PP (coagulation factors II,VII,X)	0.65 (0.21-1.3)	0.68 (0.22-1.21)	0.13
MELD	18 (6-43)	17 (2-44)	0.16
Child Pugh score (n)			0.47
A	20	51	
B	13	44	
C	9	16	
WHO performance status (0-4)	1	1	0.06
TNM stage: n, (%)			
T			0.18
1	12 (16)	51 (26)	
2	29 (38)	76 (39)	
3	31 (41)	58 (30)	
4	1 (1)	3 (2)	
Missing	3 (4)	7 (4)	
N			0.35
1	66 (87)	179 (92)	
2	3 (4)	3 (2)	
x	7 (9)	13 (7)	
M			
1	70 (92)	182 (93)	0.36
2	2 2)	12 (6)	
x	4 (6)	1 (1)	

Table II. Time intervals for patients in the two time periods for the two groups before and after implementation of the FTCP (mean (SD). A,B,C and D: See Fig. 1

	Before	After	p-value
AB: referral to first visit	16.4 (11.5) n=73	5.4 (6) n=190	<0.001
BC: first visit to clinical decision	19.9 (26.6) n=72	11.1 (13.1) n=187	0.192
AC: referral to clinical decision	34.9 (27.9) n=71	16.1 (14.4) n=190	<0.001
AD: referral to treatment	53.2 (37.9) n=48	35.9 (23.1) n=139	<0.001
CD: clinical decision to treatment	20.7 (18.4) n=49	20.4 (17.2) n=140	0.407

Table III. Survival analysis. Data reported as Hazard ratios crude and adjusted for palliative status, age, sex, liver function by MELD score and tumor status by TNM status.

	HR, Before vs. After	95% CI	p-val
Unadjusted	1.2557	(0.9499 ; 1.6510)	0.110
Adjusted for Palliative status, age, gender, MELD and T,N and M-status	0.8773	(0.6275 ; 1.2265)	0.444

after adjusting for age, gender, liver function (by MELD score), tumour status (TNM status) or palliative status (Table III).

DISCUSSION

This is the first description of the effect of the implementation of a national FTCP for HCC patients. The main finding of the study was that the FTCP reduced the time from referral to treatment mainly due to a reduction in time from referral to the first visit and time from first visit to MDT treatment decision. From the patient's perspective this is a significant improvement because diagnostic uncertainty is related to anxiety. At the same time, however, there was only an insignificant improvement in survival.

The FTCP with its shortened waiting time might improve patient satisfaction as in other cancers [12-15]. Other reports from colon cancer centers suggested a standard period of maximally two weeks from diagnostic suspicion to specialist consultation [15, 16], since any delay in diagnosis may impact the patient's well-being, mainly at the psychological level [17, 18]. The reduction in the waiting time is assumed to entail a reduction in the possible psychosocial impact on the patient caused by a period of intense anxiety and a sensation of vulnerability intervening between suspicion of cancer, definitive diagnosis and the start of treatment, a relationship supported by a number of studies [19-21].

The HCC patients in the present study were representative for the HCC patients in Denmark, but might differ from other parts of the world. Alcohol was the primary cause of cirrhosis in our patients, while HBV and HCV infections account for the majority of HCC cases in most other countries. Further, patients with advanced alcoholic cirrhosis have a poor survival even without HCC [6], which may explain the poor overall survival of these patients and the lack of survival effect of the FTCP. With median MELD scores of 17-18 and more than half of the patients being Child-Pugh B or C, the survival was not only determined by HCC. Further, a high percentage of the HCC cases (40%) were diagnosed in a non-cirrhotic liver, mostly related to obesity and NAFLD/NASH. The latter patients might present late due to lack of early symptoms and also because they are not included in screening programs, given the absence of any known underlying chronic liver disease.

In our patients, there was a trend towards prolonged overall survival after FTCP, but it was not statistically significant (p=0.11). The implementation of guidelines for fast track referral, diagnosis and treatment of other types of cancer has earlier been reported in the literature. In Catalonia (Spain) it was implemented in 2005 and led to a markedly reduced

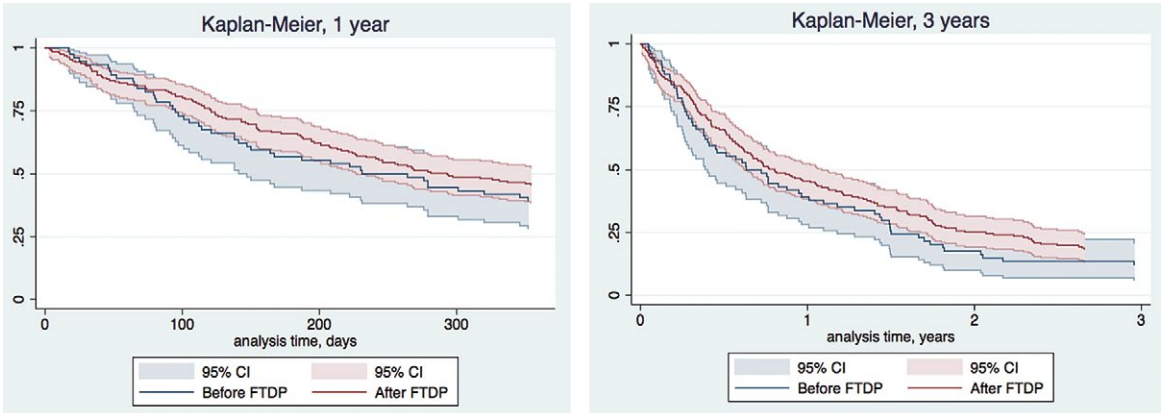

Fig. 2. Survival estimates of the 2 cohorts, before and after implementation of FTCP. 1- and 3-year survival is illustrated.

referral-to-treatment delay in breast, lung and colon cancer [22]. Our results are in accordance with other Danish studies examining the effects of FTCPs, e.g. for sarcoma, head and neck cancer and penile cancer. They have successfully reduced the waiting time [23, 24], while long-term follow-up studies are awaited to examine survival effects. Survival from colorectal cancer in Denmark improved through 2001-2012 [25], presumably due to FTCP as well as in other disease, and to stage-specific treatment improvement. As seen in lung and colon cancer patients', survival benefit might begin before the programs were launched [25, 26]. We cannot exclude the possibility that this might also play a role in our patients, resulting in only a trend towards improved survival after the FTCP implementation.

The strength of the study is the significant number of patients seen in one single multidisciplinary setting and the complete follow-up. A weakness is the retrospective design with only temporal comparisons; however, we used the same standardized CRF for all patients with a well-defined data structure and data were recorded in a consecutive manner. In addition, there was no difference regarding liver and renal function, Child-Pugh and MELD score, TNM classification, or WHO performance status between the two periods, suggesting that referral bias was of minor importance and the difference in numbers seen in the two periods rather represented more complete compliance with the guidelines by referring hospitals.

To significantly improve survival, measures to detect HCC at an earlier time point include screening of patient groups at risk. Earlier detection will allow for a more aggressive approach towards curative treatments including liver transplantation, liver resection and combination therapies of RFA and chemoembolization. Further focus on shortening waiting time and accelerating the diagnostic process of HCC are required to ensure that all patients are cared for within an acceptable time frame.

CONCLUSION

Our study showed that the implementation of FTCP for HCC patients successfully shortened the waiting time, accelerated the diagnostic process of HCC and secured acceptable course durations for more than 86% of the patients. However, this was not translated into a significant improvement in survival, but despite this the FTCP might contribute to improved comfort for the patient and a better "journey of the patient" through the healthcare system.

Conflicts of interest: None of the authors have any conflicts of interest to declare.

Authors' contributions: G.E.V, K.S. and H.G. contributed to the study design and planning, analysis of data. G.E.V. compiled and analysed data and wrote the greater part of the manuscript. H.V. and P.O. contributed to the data analysis and manuscript editing. K.S. contributed to the the statistical analysis of the data. All authors approved the final version of the manuscript.

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