Survival Rate of Cholangiocarcinoma, Hepatocellular Patients Received Cannabis Treatment

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Research Article

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Abstract

Introduction:

Cholangiocarcinoma (CCA) incidence in Northeastern Thailand is very high, and a major cause of mortality CCA patients typically have a poor prognosis and short-term survival rate, due to late-stage diagnosis. . Thailand is , the first Southeast Asian country to approve medicinal cannabis treatment, especially for palliative care with advanced cancer patients..

Patients and methods:

A retrospectively cohort comparative study of , survival rates among 491 newly diagnosed advanced CCA patients was carried out between September 2019 and 30 July, 2021; (404 patients in a standard palliative care pain management treatment group (ST), and 87 in a medicinal cannabis treatment group (CT). CCA Patients were recruited from 4 tertiary hospitals and 2 secondary hospitals in five provinces of Northeast Thailand. The cumulative survival rates were calculated by the Kaplan-Meier method, and independent prognostic factors were investigated using Cox regression.

Results:

For ST patients there was a total follow-up time of 790 person-months, with a , mortality rate of 48.35/ 100 person-years. For CT patients the total follow-up time was 476 person-months, with mortality rate of 10.9./ 100 person-years. The median survival time after registration at a palliative clinic was 0.83 months (95%CI: 0.71-0.95) for ST and 5.66 months (95%CI: 1.94-9.38) for CT None of the demographic factors were significantly associated with survival time for either ST or CT. Comparing ST with CT, there was a difference statistically significant in age, sex, cancer treatment and period of diagnosis with advanced CCA,HCC to registration factors (p-value<0.05)

Conclusions:

The medicinal cannabis group had an increase post CCA diagnosis survival rate.. Our findings support the importance of early access to palliative cannabis clinic before caner’s terminal and accelerating phase close to death.

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC/CCA) represents a rare but highly aggressive primary liver cancer featuring disease characteristics of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). The global incidence rates is around 0.59 per 1,000,000 people (1) but it is highly prevalent in Thailand.(2)The highest reported CCA incidence internationally is in Northeastem Thailand, 118.5 per 100,000, in Khon Kaen Province, which is over 100 times higher than the global rate . (3) CCAs are generally asymptomatic in early stages and are usually diagnosed late, when the disease

has already metastasized. Late-stage diagnosis limits the effective therapeutic options, and has an aggressive disease course (4) and very poor prognosis (5) resulting in lower survival rates.

Previous studies have shown the median post-diagnosis survival of CCA patients to be about 9 months (95% CI 7–11), with 1-, 3-, and 5-year survival rates at 43.4%, 21.5%, and 17.1%, respectively.(1). Mean overall survival rate at 1-, 3-, and 5-year was 66.6, 41.5, and 32.7% for patients with transitional HCC-CC (Gentile et al. 2020), with median survival time from diagnosis 4.3 months (95% CI: 3.3–5.1) (6), and after supportive treatment was 4 months (7). Survival time was increased among CCA patients receiving surgery an average of 29.38 months, best supportive treatment 5.12 months and 13.38 months for chemotherapy patients. (8)

At present, medical cannabis products are in use in many countries (9) Cannabis as a palliative treatment for cancer patients appears to be well-tolerated, effective and a safe pain-relief option with significant improvement in quality of life shown after 6 months treatment (10). In cancer patients, cannabinoids have primarily been used as a part of palliative care to alleviate pain, relieve nausea and stimulate appetite. (11), though moderate. Thailand legalized medical cannabis in February 2019, becoming the first country in Southeast Asia to regulate medical treatment (“2020 Global Cannabis Guide - Thailand | World Law Group”)https://www.theworldlawgroup.com/news/2020-global-cannabis-guide-https://www.cannabiscatalysts.com/medical-cannabis-legalization-in-thailand/ Currently, there are two treatment options for palliative cancer patients in Thailand; the standard current treatment and the new cannabis treatment. However, no studies of survival rate of medicinal cannabis treated patients from the patients’ perspective have been carried out to date.

Materials And Methods

Study design

A retrospective cohort study was conducted with 491 patients (404 received standard treatment (ST) and 87 received cannabis treatment (CT) who were diagnosed (at least by ultrasonography and treated by supportive treatment at a palliative care and/ or cannabis care clinic between 1 September 2019 and 31 December, 2020. Data was extracted from the 4 tertiary hospitals, and 2 secondary hospitals serving five provinces of Northeastem Thailand (Roi-Et Regional Hospital, Burirum Regional Hospital, Surin Provincial Hospital , Sawang Dandin Crown Prince Hospital, Panna Nikhom Hospital and Pana Hospital). The patients were followed up until death or the end of the study (30 June, 2021)

The independent variables were age at registration (Palliative clinic and/or Cannabis clinic),gender, cancer treatment and period of diagnosis to registration. The dependent variable was the post-diagnosis survival time of patients with CCA,HCC. In order to calculate the survival time, the starting point was identified as the date of registration, and the follow up period ended when a patient died or on completion of the study. Censored data were used for those still alive at the end of the study, or, lost to follow-up. The follow-up status of each patient was checked from medical records and by linkage with the death registry of the national statistics database.

Ethical approved

This study was reviewed and approved by the Maha-Sarakham University Human Research Ethics Committee (Reference NO.204/2563), and Roi-Et Regional Hospital (Reference RE064/2563), Burirum Regional Hospital Ethics Committee for Human Research, based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines (Reference No. GCP0066/2563).

Statistical methods

Descriptive statistics were used to present baseline characteristics and clinical subject data. Frequency and percentages were used to describe categorical data and means with standard deviations or medians with ranges were used to describe continuous data. The observed survival rate was calculated by the Kaplan-Meier method for median survival time with 95% confidence intervals (CIs). The log-rank test were used for comparisons between groups. The Cox proportional hazard regression model was used to assess associations between the various covariates and survival rate. The results were presented as hazard ratios (HR) with 95% confidence intervals (95%CI). The level of statistical significance was set as a p-value less than 0.05.

Results

Table 1 shows the study participants' characteristics. There were 491 patients (296 males and 195 females) with,CCA,HCC; there were 404 in the ST group (242 males and 162 females) and 87 in the CT group (54 males and 33 females). Mean ages, total particpants, ST and, CT groups, were 66.43, 66.60, 65.64 years, respectively. Most patients (43.38%) were 70 years of age. More than 71.53% in the ST received cancer chemotherapy and combinations and 52.87% of the CT group also received palliative care. Mean point of diagnosis with Advanced CCA,HCC to registration was 8.65 months for ST, and 5.32 months for CT. Most patients (38.49%) were registered at the palliative and / or cannabis care clinic and 94.60% (ST), 59.80% (CT) had died by the end of the study. The total follow-up time For ST patients was 790 person-months, with a mortality rate of 48.35/ 100 person-years. For the CT group follow-up was, 476 person-months, for a mortality rate of 10.9./ 100 person-years for CT.

Table 1
Baseline characteristics of included patients

Variable	Patient Treatment Group		
	All (n=491,%)	Standard(n=404,%)	Cannabis(n=87,%)
Age ,year (mean,S.D.)	66.43 (11.36)	66.60 (11.67)	65.64 (9.82)
< 60	129 (26.27)	105 (25.99)	24 (27.59)
60 – 69	149 (30.35)	121 (29.95)	28 (32.18)
≥ 70	213 (43.38)	178 (44.06)	35 (40.23)
Sex			
Male	296 (60.29)	242 (59.99)	54 (62.07)
Female	195 (39.71)	162 (40.01)	33 (37.93)
Cancer Treatment			
Surgery	32 (6.52)	28 (6.93)	4 (4.59)
Chemotherapy	158 (32.18)	140 (34.65)	18 (20.70)
Combine	171 (34.83)	149 (36.88)	22 (25.29)
Palliative care	130 (26.47)	87 (21.54)	43 (49.42)
Period advanced diagnosis to register (mean,S.D.)	6.05 (2.63)	6.12(2.55)	5.46(2.94)
< 3 months	100 (20.37)	60 (14.85)	40 (45.98)
3-6 months	226 (46.02)	204 (50.49)	22 (25.28)
6-9 months	102 (20.77)	94 (23.27)	8 (9.20)
> 9 months	63 (12.84)	46 (11.39)	17 (19.54)
Status at the end of study	434 (88.40)	382 (94.60)	52 (59.80)
Dead			

Table 2
Survival Rates of Patients receiving Standard treatment vs Cannabis treatment

Survival time	Survival rate (%)(95%CI)		
	Overall	Standard(n = 404)	Cannabis(n = 87)
3 months	23.90(20.22-27.76)	28.80(24.72-32.99)	60.48(49.35-69.91)
6 months	14.61(11.64-17.48)	20.00(16.35-23.92)	48.63(36.78-57.70)
9 months	10.48(7.75-13.68)	16.50(12.86-20.55)	35.73(23.83-47.74)
12 months	9.27(6.62-12.42)	15.75(12.04-19.92)	29.98(18.15-42.73

Table 3
Factors Effecting Survival Rates of patients receiving Standard Treatment

Variables	n=404	MST (95%CI)	Person-months	IR/100	HR(95%CI)	p-value
Age ,year						0.26
< 60	104	0.83(0.62-1.03)	170	0.59	1	
60 – 69	122	0.93(0.73-1.03)	244	0.47	0.81(0.62-1.06)	
≥ 70	178	0.83(0.67-1.20)	375	0.44	0.83(0.65-1.07)	
Sex						0.10
Male	242	0.73(0.67-0.93)	427	0.53	1	
Female	162	0.97(0.83-1.33)	362	0.42	0.84(0.68-1.04)	
Cancer Treatment						0.062
Surgery	27	1.33(0.3-2.50)	106	0.20	1	
Chemotherapy	139	0.93(0.73-1.0)	209	0.65	1.7(1.04-2.68)	
Combine	150	0.83(0.67-1.27)	311	0.45	1.42(0.90-2.23)	
Palliative care	88	0.73(0.5-0.93)	162	0.51	1.66(1.04-2.67)	
Period diagnosis to register						0.25
< 3 months	64	0.93(0.67-1.50)	113	0.54	1	
3-6 months	200	0.83(0.67-0.97)	406	0.46	1.01(0.75-1.34)	
6-9 months	94	1.07(0.67-1.67)	210	0.41	0.84(0.61-1.17)	
> 9 months	46	0.67(0.44-1.77)	59	0.72	1.21(0.82-1.77	
MST= Median survival time						

Table 4
Factors Effecting Survival Rates of patients receiving Cannabis Treatment

Variables	n=87	MST (95%CI)	Person-months	IR/100	HR(95%CI)	p-value
Age ,year						0.64
< 60	24	5.67(2.87-15.0)	147	0.08	1	
60 – 69	28	3.27(2.0-12.0)	128	0.13	1.41(0.68-2.92)	
≥ 70	35	6.0(2.33-10.03)	200	0.11	1.23(0.62-2.45)	
Sex						0.44
Male	54	6.0(3.07-10.03)	300	0.10	1	
Female	33	3.5(1.77-9.5)	175	0.11	1.24(0.71-2.16)	
Cancer Treatment						0.19
Surgery	4	2.0(1.83-10)	14	0.21	1	
Chemotherapy	18	9.50(5.17-15)	139	0.06	0.36(0.09-1.37)	
Combine	20	7.0(1.67-15)	121	0.09	0.51(0.14-1.84)	
Palliative care	45	3.07(2.17-8.33)	201	0.14	0.74(0.22-2.46)	
Period diagnosis to register						0.54
< 3 months	40	3.17(2.17-9)	113	0.54	1	
3-6 months	22	8.17(2.87-15)	406	0.46	1.01(0.75-1.34)	
6-9 months	8	5.0(0.73-8)	210	0.41	0.84(0.61-1.17)	
> 9 months	17	5.17(2.0-9.0)	59	0.72	1.21(0.82-1.77)	
MST= Median survival time						

Table 5
Survival Rates of patients receiving Standard treatment vs Cannabis treatment

subgroup	Overall	Standard(n = 404)	Cannabis(n = 87)	P Value
Overall survival	1.10 (0.89-1.30)	0.83 (0.71-0.95)	5.66(1.94-9.38)	< 0.001
Age ,year				< 0.001
< 60	1.00(0.77-1.22)	0.83(0.62-1.03)	5.67(2.87-15.0	
60 – 69	1.16(0.79-1.54)	0.93(0.73-1.03)	3.27(2.0-12.0)	
≥ 70	1.26(0.94-1.58)	0.83(0.67-1.20)	6.0(2.33-10.03)	
Sex				< 0.001
Male	1.00(0.78-1.21)	0.73(0.67-0.93)	6.0(3.07-10.03)	
Female	1.33 (1.06-1.60)	0.97(0.83-1.33)	3.5(1.77-9.5)	
Cancer Treatment				< 0.001
Surgery	1.83(0.52-3.14)	1.33(0.3-2.50)	2.0(1.83-10)	
Chemotherapy	1.00(0.81-1.18)	0.93(0.73-1.0)	9.50(5.17-15)	
Combine	1.16(0.79-1.53)	0.83(0.67-1.27)	7.0(1.67-15)	
Palliative care	1.26(0.92-1.60)	0.73(0.5-0.93)	3.07(2.17-8.33)	
Period diagnosis to register				<0.001
< 3 months	1.56(1.26-1.86)	0.93(0.67-1.50)	3.17(2.17-9)	
3-6 months	1.00(0.78-1.21)	0.83(0.67-0.97)	8.17(2.87-15)	
6-9 months	1.33(0.80-1.86)	1.07(0.67-1.67)	5.0(0.73-8)	
> 9 months	1.00(0.79-1.20)	0.67(0.44-1.77)	5.17(2.0-9.0)	

,3,4,5 and Figures 1-5 present the survival rate data. after registration at either the palliative or cannabis care clinic. The cumulative 3, 6, 9 and 12 months survival rates were 28.80% (95% CI: 24.72-32.99), 20.00% (95% CI: 16.35-23.92), 16.50% (95% CI: 12.86-20.55) and 15.75% (95% CI: 12.04-19.92) for ST, 60.48(95% CI: 49.35-69.91), 48.63(95% CI: 36.78-57.70), 35.73(95% CI: 23.83-47.74) and 29.98(95% CI: 18.15-42.73 for CT, respectively. The median duration of survival was 0.83 months (95%CI: 0.71-0.95) for ST and 5.66 months (95%CI: 1.94-9.38) for CT. None of the demographic factors were significantly associated with survival time for either ST or CT. Comparing ST with CT, there was a statistically significant difference in age, sex, cancer treatment and period diagnosis with advanced CCA,HCC to register factors (p-value<0.05)

Discussion

In the present study, we reported the impact of two types of treatment that affect the survival of CCA,HCC patients who either had supportive treatment at palliative clinic,, or, a cannabis clinic. CT was the most effective treatment, with an overall survival time of 5.66 months, while overall survival time was 0.83 months for ST. Meanwhile, The overall survival times are consistent with other findings for after supportive treatment (12) where survival time was only 4.3 months post-diagnosis. Patients diagnosed at an advanced stage were twice as likely to die (HR: 1.8, 95%CI: 1.1-2.9), (13) In contrast Advanced cancer patients using cannabis showed a significantly decreased overall survival (OS) compared to nonusers. The median OS for cannabis use was 6.4 months (95% CI,3.2–9.7) and 28.5 months (95% CI, 15.6-NA) for non-users (14)

In the univariate analysis, cancer treatment and period of diagnosis with advanced CCA,HCC to registration were associated with survival rate. It was found that the ST registered patients survived less than 3 months after being diagnosed with advanced-stage CCA,HCC., maybe because patients who will have to be consulted by a oncologist and other doctors who is the main physician in taking care of patients before The patients were registered and received supportive treatment at Palliative clinic, along with most of the patients undergoing a combination of surgery, chemotherapy, and a combination of treatments before being admitted to Palliative clinic, while the registered patients at Cannabis clinic were > 70 years, no cancer treatment and supportive treatment at Cannabis clinic, especially at community hospitals where CT / MRI / biopsy / US has been shown to have advanced organ metastases. another will receive treatment at Cannabis clinic without waiting for a consult from the oncologist and found that patients were able to receive chemotherapy along with cannabis

This study has several limitations. One is the number of patients who dropped out before study completion Level of disease progression may explain this for a number of patients. Most patients suffered from advanced cancers and received heavy oncological treatments and were elderly. Patients with CCA have poor prognosis and short-term survival at the time of diagnosis. Registration, and decision-making at the standard and / or cannabis clinic in each hospital differs across physicians, patients, families, stages of disease, organ metastasis, methods of treatment, and severity of symptoms.

To the best of our knowledge, this is the first study that has compared survival rate and quality of life of CCA,HCC patients who received either ST, or, CT. across tertiary and secondary hospitals and across 5 provinces. Medical cannabis used in this study were standardized cannabis preparations made by the Thailand Food and Drug Administration. The side effects, safety, benefits and harms of the cannabis produced have been reviewed and are considered appropriate patient treatment. Prescribing doctors are trained, registered prescribers of medical cannabis

Abbreviations

QOL
quality of life
ST

standard treatment
CT
cannabis treatment

Declarations

Conflict of interest

None declared.

Supplementary Information

The online version contains supplementary material available

https://docs.google.com/spreadsheets/d/1Z_d0MrA2eFe3HXUDPlgG94OgE84yiKsE/edit?usp=sharing&ouid=115363787239545343161&rtpof=true&sd=true

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Statement

All methods were carried out in accordance with relevant guidelines and

regulations.

Authors' contributions

Not applicable.

Authors' information

Not applicable.

Funding

None declared.

Availability of data and materials

Patient's data were available in medical records room of the Roi-Et Regional Hospital, Burirum Regional Hospital, Surin Provincial Hospital , Sawang Dandin Crown Prince Hospital, Panna Nikhom Hospital and Pana Hospital. The datasets generated and/or analysed during the current study are not publicly available due to they are files in medical records room in our hospital, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was reviewed and approved by the Maha-Sarakham University Human Research Ethics Committee (Reference NO.204/2563), Because of its retrospective manner, informed consent was waived by the Roi-Et Regional Hospital (Reference RE064/2563), Burirum Regional Hospital).

Consent for publication

Not applicable.

Competing interests

The authors indicated no potential conficts of interest.

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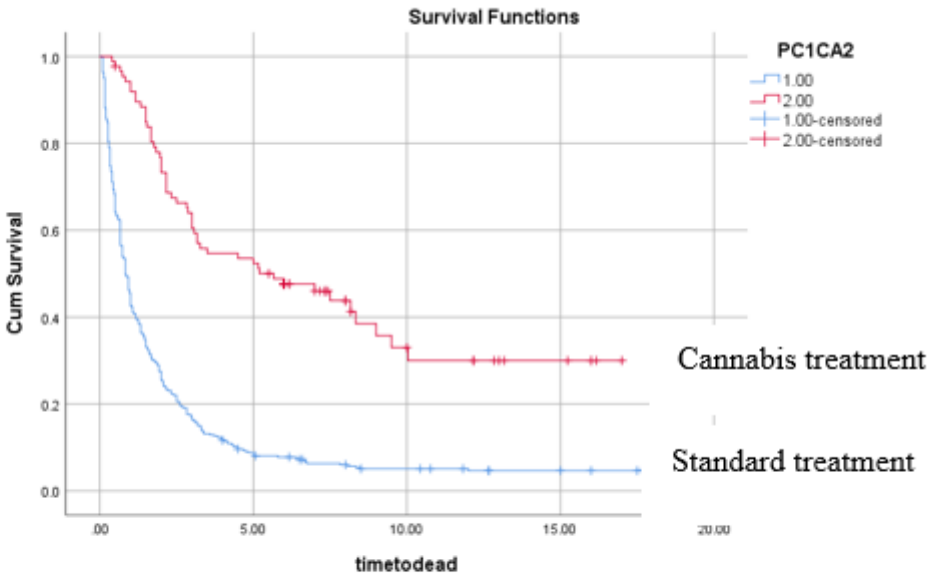
Figures

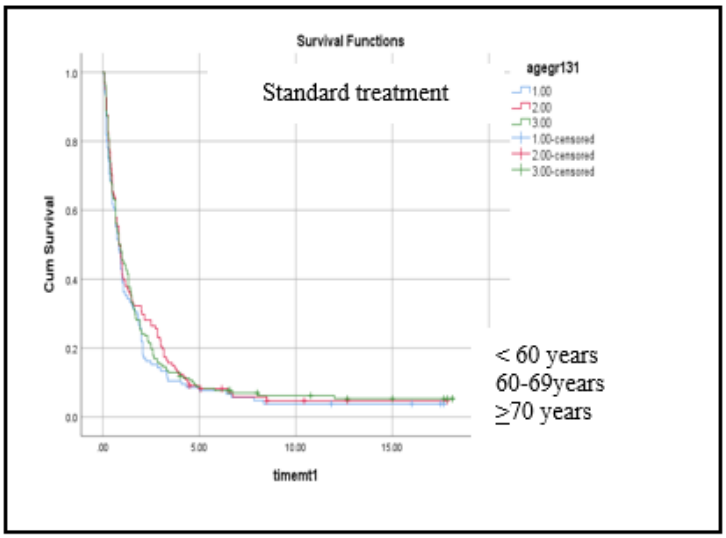


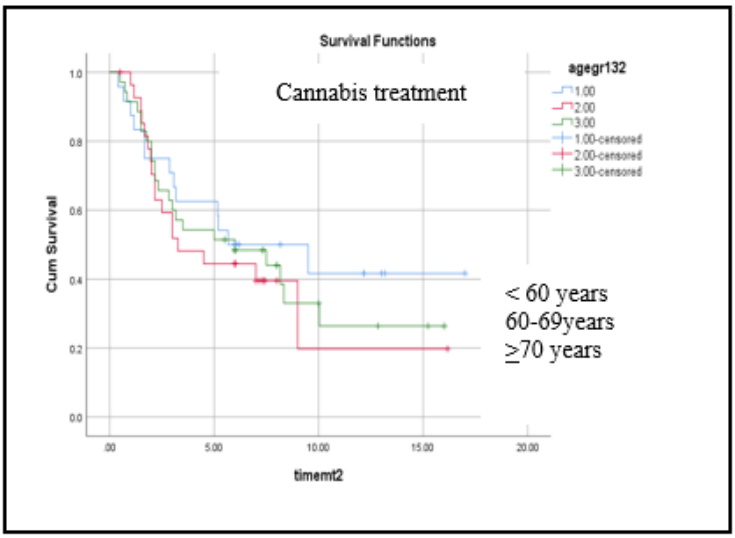
No at Risk

404	33	15	8
87	45	10	4

Figure 1

Comparison of overall survival period of advanced diagnosis to register :< 3 months, 3-6 months,6-9 months,> 9 months between standard treatment vs cannabis treatment





No at Risk

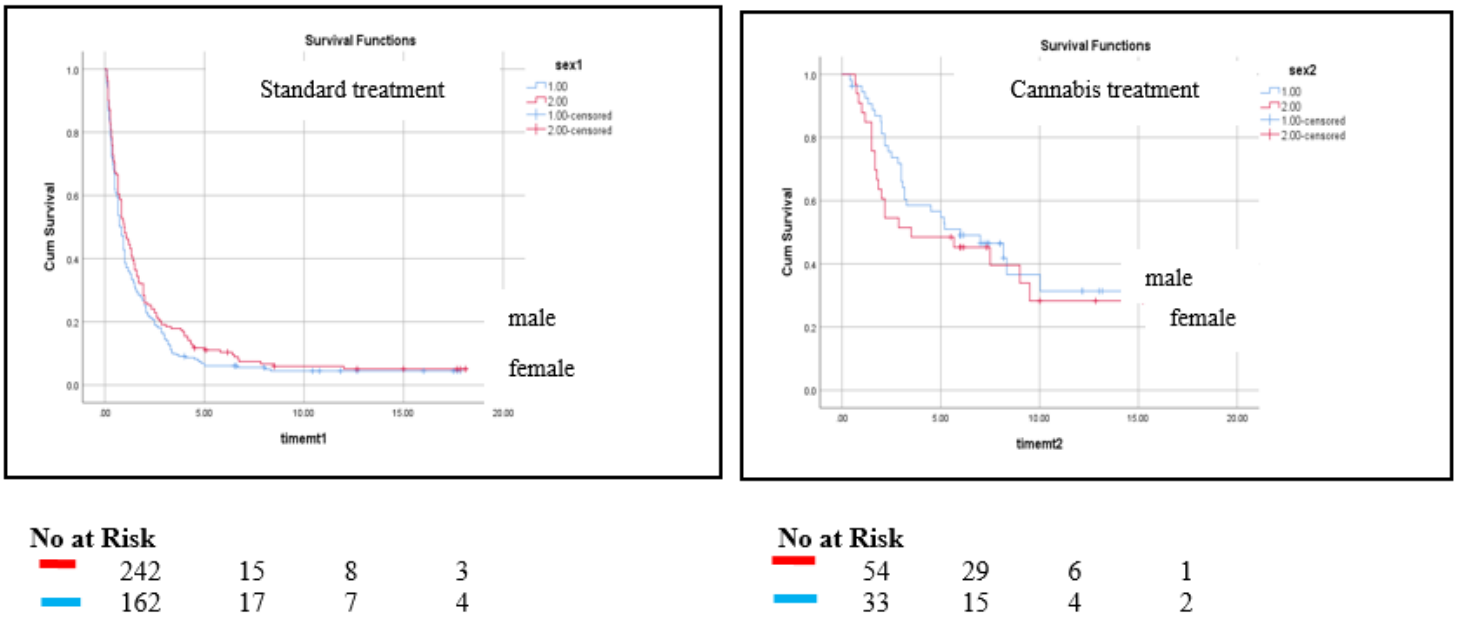
105	8	4	3
121	9	3	0
178	14	8	4

No at Risk

24	15	4	1
28	12	1	1
35	18	5	3

Figure 2

Comparison of overall survival between Standard treatment vs Cannabis treatment

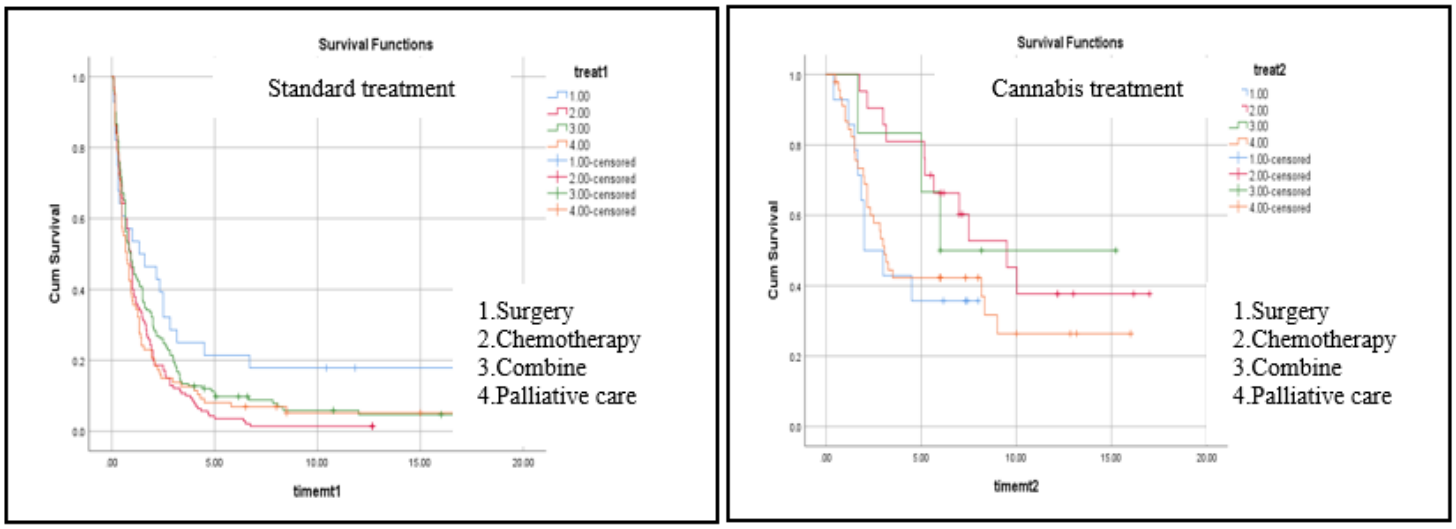


No at Risk			
242	15	8	3
162	17	7	4

No at Risk			
54	29	6	1
33	15	4	2

Figure 3

Comparison of overall survival period of age < 60 y , 60-69 y, ≥70 y between Standard treatment vs Cannabis treatment

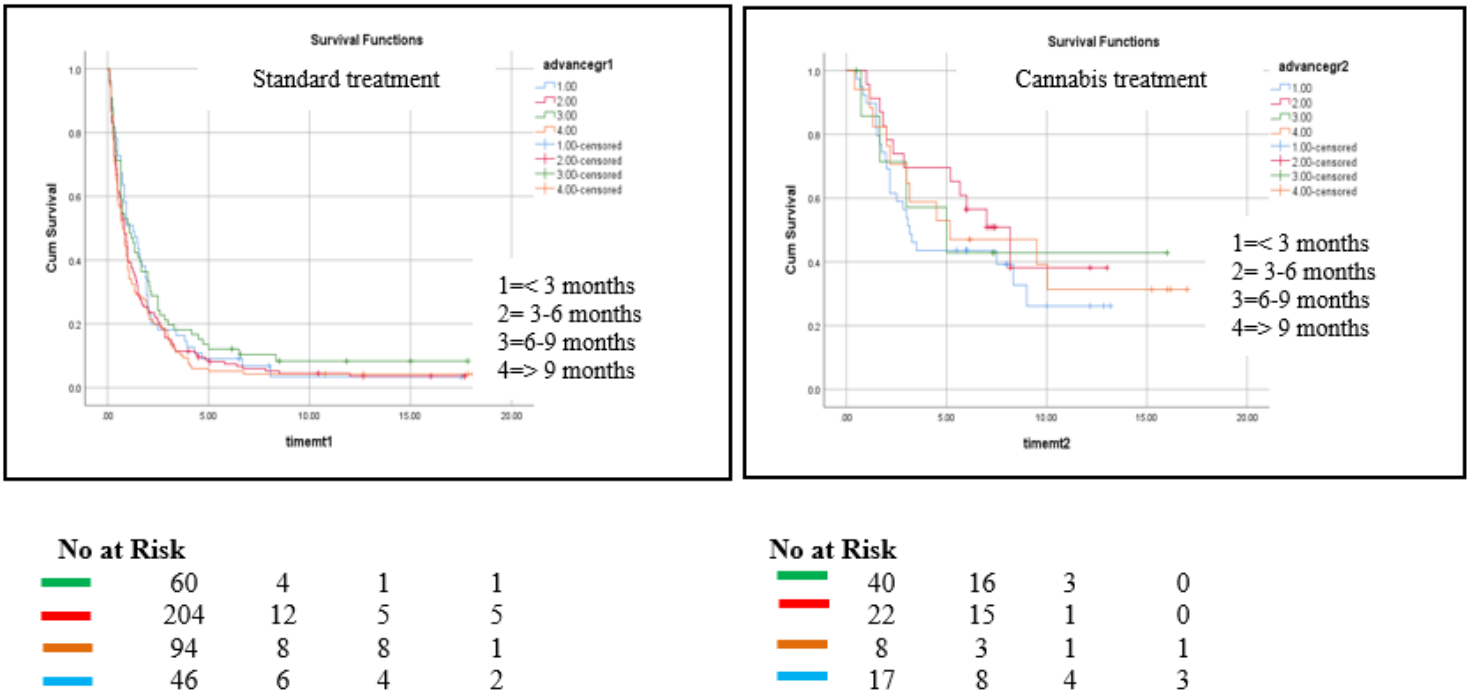


No at Risk			
28	6	4	2
140	5	1	0
149	14	6	3
87	7	2	0

No at Risk			
4	1	0	0
18	13	5	1
22	12	2	1
43	18	5	1

Figure 4

Comparison of overall survival period of cancer treatment ; surgery,chemotherapy,combine ,palliative care between standard treatment vs cannabis treatment



No at Risk

	60	4	1	1
	204	12	5	5
	94	8	8	1
	46	6	4	2

No at Risk

	40	16	3	0
	22	15	1	0
	8	3	1	1
	17	8	4	3

Figure 5

Comparison of overall survival period of advanced diagnosis to register :< 3 months, 3-6 months,6-9 months,> 9 months between standard treatment vs cannabis treatment