LIPIODOL ACCUMULATION PATTERN AS IMAGING BIOMARKER OF TUMORAL RESPONSE AFTER CONVENTIONAL TRANSARTERIAL CHEMOEMBOLIZATION AND SURVIVAL OUTCOME IN HEPATOCELLULAR CARCINOMA PATIENTS

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DISCLAIMER

I declare that this dissertation records the results of the study performed by me and that it is of my own composition.

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(MOHD YADIE SYAZWAN BIN AZIZI)

Date:

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

AFP	Alpha-Fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CLT	Cadaveric liver transplant
CPS	Child-Pugh Score
cTACE	Conventional transarterial chemoembolization
DEB-TACE	Drug-eluting beads transarterial chemoembolization
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HUSM	Hospital Universiti Sains Malaysia
LDLT	Living donor liver transplant
PEI	Percutaneous ethanol injection
PS	Performance status
RECIST	Response evaluation criteria in solid tumors
SIRT	Selective internal radiotherapy
TACE	Transarterial chemoembolization
WHO	World Health Organization

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ABSTRAK

Latar belakang: TACE adalah rawatan pilihan untuk karsinoma hepatoselular yang tidak dapat dibedah dan prosedur yang berjaya akan meningkatkan kadar kelangsungan hidup pesakit. Liputan antitumoral yang baik pada tumor hati yang disasarkan adalah diperlukan untuk menghasilkan nekrosis tumor yang baik dan menghasilkan kesan terapi yang baik. TACE dengan menggunakan campuran antikanser dan minyak beriodine (Lipiodol) dapat memberikan gambaran keseluruhan mengenai tahap pengumpulan dan pengekalan ubat di dalam tumor yang disasarkan yang di kenal pasti pada pemeriksaan CT-scan yang berikutnya, sekaligus dapat meramalkan hasil rawatan. Kajian ini bertujuan untuk mengetahui hubungan antara pola akumulasi lipiodol dan tindak balas tumor yang disasarkan terhadap rawatan yang diberikan, dan kadar kelangsungan hidup keseluruhan pesakit HCC.

Metod: Kajian rekod retrospektif ini dilakukan dari tahun 2013 hingga 2020 pada pesakit yang menerima TACE dengan menggunakan ubat antikanser dan Lipiodol di Hospital Universiti Sains Malaysia, yang memenuhi kriteria inklusi dan pengecualian. Corak pengumpulan lipiodol diperhatikan kira-kira selepas enam minggu selepas TACE pada imbasan CT susulan dan kemudian dikelaskan kepada 4 corak pengumpulan; corak 4, pengumpulan lengkap; corak 3, kuat (> 75% daripada jumlah tumor); corak 2, sederhana (<75% daripada jumlah tumor); dan corak 1 - pengumpulan rendah. Penilaian tindak balas tumor dilakukan mengikut kriteria mRECIST. Ujian Chi-Square atau Fischer Exact dan analisis ujian regresi logistik berganda digunakan untuk menentukan hubungan antara corak pengumpulan lipiodol dan tindak balas tumor terhadap rawatan. Ujian analisis kelangsungan hidup (analisis Kaplan-Meier) digunakan untuk menentukan hubungan antara corak akumulasi dan keseluruhan kelangsungan hidup pesakit yang menerima TACE. Ujian Regresi Bahaya Berkadar Sederhana dan Berbilang Cox

digunakan untuk mengkaji faktor-faktor lain yang berkaitan dengan kelangsungan hidup keseluruhan.

Hasil: Sebanyak 38 subjek diperoleh dalam kedua-dua kumpulan BCLC tahap B (n = 33) dan tahap BCLC C (n = 10). Pada tahap BCLC B, 18% (n = 7) berada dalam akumulasi lengkap, 26% (n = 10) dalam pengumpulan intensif, 16% (n = 6) dalam akumulasi sederhana dan 13% (n = 5) dalam corak akumulasi rendah. Ujian tepat Fisher untuk subjek BCLC tahap B menunjukkan hubungan yang signifikan antara corak akumulasi lipiodol dan tindak balas tumor dengan nilai Fisher Tepat 27.025 (p <0.001). Ujian Spearman-rho melaporkan hubungan signifikan corak pengumpulan lipiodol dan tindak balas tumor dengan magnitud 0,84 dalam kumpulan ini. Pada tahap BCLC C tidak ada pola akumulasi lengkap yang diamati, 5% (n = 2) berada dalam akumulasi intensif, 11% (n = 4) berada dalam akumulasi sederhana dan 11% (n = 4) berada dalam pola akumulasi rendah. Ujian tepat Fisher untuk subjek di BCLC Tahap C menunjukkan tidak ada hubungan yang signifikan antara corak pengumpulan lipiodol dan tindak balas tumor dengan nilai Tepat Fisher 2.281 (p> 0.05). Analisis kelangsungan hidup menunjukkan bahawa jumlah kes yang lebih tinggi dapat bertahan pada 1 tahun dan 3 tahun sepenuhnya (85.7% pada 1 tahun dan 17.1% pada 3 tahun) dan sengit (88.9% pada 1 tahun dan 38.1% pada 3 tahun) kumpulan pengumpulan lipiodol pada kumpulan BCLC tahap B berbanding dengan corak pengumpulan yang lain. Survival median dalam kumpulan BCLC B untuk setiap kumpulan adalah 26 bulan (lengkap), 30 bulan (intens), 9 bulan (sederhana) dan 16 bulan (rendah). Pada kumpulan BCLC C di mana hanya corak akumulasi sederhana dan rendah yang diperhatikan di atas satu tahun, dengan kadar survival 1 tahun adalah 50% (sederhana) dan 25% (rendah) dengan tidak ada yang bertahan pada tiga dan lima tahun.Masa survival median untuk kumpulan BCLC tahap C adalah enam bulan (intens), empat bulan (sederhana), dan lapan bulan (rendah). Analisis regresi cox sederhana dan berganda

menunjukkan bahawa bilangan kumpulan nodul hati dan jumlah prosedur TACE yang dilakukan adalah antara faktor kematian prognostik yang signifikan dalam HCC. Pesakit yang mempunyai 5-9 nodul hati mempunyai risiko kematian 12.1 kali lebih tinggi berbanding dengan kumpulan pesakit dengan 1-4 nodul hati (HR: 12.1, 95% CI: 1.17 - 124.57). Pesakit yang menerima satu prosedur TACE mengalami penurunan risiko kematian sebanyak 0,57 (HR: 0,565, 95% CI: 0,393 - 0,812). Walaupun analisis regresi tambahan tidak melaporkan pengaruh signifikan pola akumulasi lipiodol pada perkembangan penyakit, analisis korelasi melaporkan korelasi positif sederhana antara pola akumulasi lipiodol dan perkembangan penyakit (r_s (36) = 0,796, $p < 0,001$).

Kesimpulan: Pengumpulan lipiodol pada tumor hati dapat dinilai menggunakan ciri pengimejan garis dasar kuantitatif dan ini menunjukkan korelasi yang signifikan dengan tindak balas tumor terhadap rawatan dan mempengaruhi hasil kelangsungan hidup pesakit. Kajian kami mengesahkan penemuan kajian sebelumnya dan mengesahkan sifat unik dan fungsi Lipiodol sebagai agen biomarker khusus tumor, pembawa ubat, dan pengimejan untuk merawat pesakit HCC.

Kata kunci: TACE, lipiodol, pola retensi lipiodol, karsinoma hepatoselular.

ABSTRACT

Background: TACE is the locoregional treatment of choice for unresectable hepatocellular carcinoma, and a successful procedure would improve the survival rate of the patient. Good antitumoral coverage in the targeted liver tumor is necessary to produce good tumoral necrosis and results in a good therapeutic effect. TACE by using a mixture of anticancer and iodized oil (Lipiodol) may provide an overview of the degree of accumulation and retention within the targeted tumor on subsequent CT-scans follow up, thus predicting the outcome of the treatment. This study aimed to determine the correlation between the pattern of accumulation pattern of lipiodol and the targeted tumoral response toward the treatment given and the overall survival rate of HCC patients.

Methods: This retrospective record review was done from 2013 until 2020 in patients who received TACE with anticancer and Lipiodol in Hospital Universiti Sains Malaysia, who are fulfilling inclusion and exclusion criteria. Lipiodol accumulation pattern is observed approximately after six weeks post-TACE on the follow-up CT scans and later is classified into 4 accumulation patterns; pattern 4, complete accumulation; pattern 3, intense (>75% of tumor volume); pattern 2, moderate (<75% of tumor volume); and pattern 1 – low accumulation. Evaluation of the tumoral response was done according to the mRECIST criteria. Chi-Square or Fischer Exact test and multiple logistic regression test analysis was used to determine the association between the lipiodol accumulation pattern and the tumor response towards the treatment. A survival analysis test (Kaplan-Meier analysis) was used to determine the association between the accumulation pattern and the overall survivability of the patient who received TACE. Simple and Multiple Cox Proportional Hazard Regression tests were used to study other associated factors affecting overall survivability.

Results: A total of data from 38 subjects were obtained in both BCLC stage B (*n*=33) and BCLC stage C (*n*=10) groups. In BCLC stage B, 18% (*n*=7) were in complete accumulation, 26% (*n*=10) in intense accumulation, 16% (*n*=6) in moderate accumulation and 13% (*n*=5) in low accumulation pattern. Fisher's exact test for BCLC stage B subjects showed significant association between lipiodol accumulation pattern and tumor response with Fisher's Exact value of 27.025 ($p<0.001$). Spearman-rho test reports a significant association of lipiodol accumulation pattern and tumor response with a magnitude of 0.84 in this group. In BCLC stage C no complete accumulation pattern was observed, 5% (*n*=2) were in intense accumulation, 11% (*n*=4) were in moderate accumulation and 11% (*n*=4) were in low accumulation pattern. The Fisher's exact test for subjects in BCLC Stage C showed no significant association between lipiodol accumulation pattern and tumor response with Fisher's Exact value 2.281 ($p>0.05$). Survival analysis shows higher proportion of cases survived at 1-year and 3-year in complete (85.7% at 1-year and 17.1% at 3-year) and intense (88.9% at 1-year and 38.1% at 3-year) lipiodol accumulation group in BCLC stage B group as compared to other accumulation patterns. The median survival time in BCLC stage B for each group were 26 months (complete), 30 months (intense), 9 months (moderate) and 16 months (low). In BCLC stage C group where only moderate and low accumulation pattern were observed above one year, with 1-year survival rate was 50% (moderate) and 25% (low) with none survive at three and five years. The median survival time for BCLC stage C group were six months (intense), four months (moderate), and eight months (low). Simple and Multiple cox regression analysis revealed that the number of liver nodules group and number of TACE procedures done were among significant prognostic factor of death in HCC. Patients that have 5-9 liver nodules had a 12.1 times higher risk of death as compared to the group of patients with 1-4 liver nodules (HR: 12.1, 95% CI: 1.17 – 124.57). Patients that received one TACE procedure are expected to have a decrease in risk of death by 0.57 (HR: 0.565, 95% CI: 0.393 – 0.812). Though

additional regression analysis did not report a significant influence of lipiodol accumulation pattern on disease progression, correlation analysis reported a moderate positive correlation between lipiodol accumulation pattern and disease progression ($r_s(36) = 0.796$, $p < 0.001$).

Conclusion: Lipiodol deposition in liver tumors can be evaluated using quantitative baseline imaging characteristics and it shows significant correlation with tumor response toward the treatment and influence the survival outcome of the patients. Our study confirms the findings of previous studies and validates the unique properties and function of Lipiodol as a tumor-specific, drug-carrying, and imaging biomarker agent to treat HCC patients.

Keywords: TACE, Lipiodol, Lipiodol accumulation, hepatocellular carcinoma.