The feasibility of transcatheter arterial chemoembolization following radiation therapy for hepatocellular carcinoma

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(Degree)
博士（医学）

(Date of Degree)
2021-09-25

(Resource Type)
doctoral thesis

(Report Number)
甲第8151号

(URL)
https://hdl.handle.net/20.500.14094/D1008151

(課程博士関係)

学 位 論 文 の 内 容 要 旨

The feasibility of transcatheter arterial chemoembolization following radiation therapy for hepatocellular carcinoma

肝細胞癌に対する放射線治療後の経動脈的化学塞栓療法の安全性

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Introduction: Hepatocellular carcinoma (HCC) is a leading cause of global cancer-related death. Recent technological developments facilitated the delivery of large doses to the tumor, while avoiding the healthy liver parenchyma around. This has led to an increased usage of RT for the treatment of HCC, often for the treatment of macrovascular invasion (MVI) associated with HCC. Additional uses include as a palliative therapy for patients with poor prognostic features or with physical or technical unavailability to other treatments. TACE may be required later in patients treated with RT because of the high recurrence rate and multinodular presentation of HCC.

Purpose: The aim of this study was to assess the feasibility of TACE following RT. The risk of liver function impairment and mortality associated with cumulative treatment was evaluated.

Materials and Methods: In this retrospective cohort study, we reviewed the records of 67 patients between January 2012 and December 2018 who underwent TACE following RT and met the inclusion exclusion criteria.

The patients underwent a 3D conformal radiation therapy (3DCRT) or stereotactic radiation therapy (SRT). Conventional TACE (cTACE) or drug eluting beads (DEB-TACE) was determined by consensus between interventional radiologists and hepatologists, was based on the number, size, and distribution of lesions and the global liver function of the patients.

The study outcomes comprised: impairment in liver function defined as Child-Turcotte-Pugh (CTP) by ≥2 points at 1 month, incidence of major complications, survival duration, and short-term mortality within 6 months after TACE

Results: The mean age of the enrolled patients was 73.5 years with majority of them belong to Barcelona clinic liver cancer stage C (68.7%). The duration between RT and TACE was between 0.03 and 30.5 months.

Short-term liver function impairment, defined as an increase in CTP score by ≥ 2 points occurred in eight patients (11.9%). Neither abscess nor biloma was detected within a month.

Nine patients died within 6 months following TACE, none of them within the first month following TACE.

The mean liver dose (MLD) was a significant predictor of liver function impairment at 1 month (P=0.042). Low liver functional reserve, distant metastasis (P=0.037), MLD (P=0.046), TACE type (P=0.025), and TACE within 3 months following RT (P=0.007) were significant predictors of short-term mortality.

Discussion: TACE poses a substantial risk of liver function impairment and is not beneficial for patients with poor hepatic reserve. Previous studies reported a deterioration in the liver function in 11-24.5% of patients with an increase in CTP score by ≥2 points following TACE unpreceded with RT. This rate is comparable to ours (11.9%); hence, TACE following RT does not exacerbate the effect of liver function. Furthermore, it may be safe in terms of liver function impairment at 1 month.

The median and mean survival after sequential TACE in the present study were 17.5. and 25.6 months, respectively. This short survival can be attributed to the poor clinical status of the patients, as 68.7% of the patients was BCLC stage C. Despite their poor clinical conditions, the median survival duration was 17.5 months. This was relatively longer than the 14 months reported in a previous study, which included unresectable patients with HCC, predominantly with stage B BCLC, following TACE without RT.

Survival rate of 71-81% at 6 months following TACE was previously reported. Mortality within the first month was reported 0-10%. The early mortality within 6 months is comparable to that reported in previous studies, in which TACE was performed without RT. Thus, TACE in patients underwent RT might be feasible with respect to both survival and short-term mortality and could be a treatment option for advanced HCC.

Biloma and liver abscess are well-known post TACE complications, with reported incidences of up to 3.3% and 2.5%, respectively. Additionally, dilatation of the bile duct and the formation of biloma often occur following RT. Therefore, the rate of biloma and liver abscess would likely increase after the sequential therapy, compared to either RT or TACE alone. However, we could not detect the above-mentioned complications in the cohort even when TACE was combined with RT. This result highlights the safety of performing TACE about local complications in patients who received liver RT earlier.

RT for the liver is reportedly associated with the risk of RILD and MLD predicts its development. MLD was reported a significant risk factor for increase in CTP score following SRT. The MLD of RT was found to be a significant predictor of short-term liver function impairment at 1 month following TACE. Thus, it is important to assess the MLD before TACE; the risk for a potential liver deterioration should be carefully evaluated when the MLD is high.

RILD occurs as an acute response during or within a few weeks of RT, or as a late response, months to years after the completion of RT, resulting in liver function impairment. In our study, short duration between RT and TACE (3 months) was a significant risk factor of liver

deterioration and short-term mortality in this study. It is presumed that TACE caused further liver damage when RILD was still ongoing Thus, the short interval between RT and the following TACE may be considered a risk factor, highlighting the need to evaluate the interval between TACE and preceding RT.

This study had some limitations: the study design was retrospective, relatively small sample size, coexisting medical conditions and systemic therapy were not sufficiently assessed.

In conclusion, performing TACE following liver RT poses no more risks than TACE alone, with comparable rates of short-term liver impairment and severe complications. This sequential treatment may be feasible. However, more attention should be paid to situations when there is an impairment of the pre-treatment liver function or after a high-dose RT. Moreover, it is advisable to delay TACE until RILD subside.

論文審査の結果の要旨			
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論文題目 Title of Dissertation	肝細胞癌に対する放射線治療後の経動脈的化学塞栓療法の安全性 The feasibility of transcatheter arterial chemoembolization following radiation therapy for hepatocellular carcinoma		
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（要旨は１，０００字～２，０００字程度）

Background and Aims

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Background and Aims

In this retrospective cohort study, we reviewed the records of 67 patients between January 2012 and December 2018 who underwent TACE following RT and met the inclusion exclusion criteria. The patients underwent a 3D conformal radiation therapy (3DCRT) or stereotactic radiation therapy (SRT). Conventional TACE (cTACE) or drug eluting beads (DEB-TACE) was determined by consensus between interventional radiologists and hepatologists, was based on the number, size, and distribution of lesions and the global liver function of the patients.

The study outcomes comprised: impairment in liver function defined as Child-Turcotte-Pugh (CTP) by ≥2 points at 1 month, incidence of major complications, survival duration, and short-term mortality within 6 months after TACE.

Results

The mean age of the enrolled patients was 73.5 years with majority of them belong to Barcelona clinic liver cancer stage C (68.7%). The duration between RT and TACE was between 0.03 and 30.5 months.

Short-term liver function impairment, defined as an increase in CTP score by ≥ 2 points occurred in eight patients (11.9%). Neither abscess nor biloma was detected within a month.

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The mean liver dose (MLD) was a significant predictor of liver function impairment at 1 month (P=0.042). Low liver functional reserve, distant metastasis (P=0.037), MLD (P=0.046), TACE type (P=0.025), and TACE within 3 months following RT (P=0.007) were significant predictors of short-term mortality.

Discussion

TACE poses a substantial risk of liver function impairment and is not beneficial for patients with poor hepatic reserve. In this study, TACE following RT does not exacerbate the effect of liver function. Despite their poor clinical conditions, the median survival duration was relatively longer than a previous study, which included unresectable patients with HCC following TACE without RT. The early mortality within 6 months is comparable to previous studies, in which TACE was performed without RT. Thus, TACE in patients underwent RT might be feasible with respect to both survival and short-term mortality and could be a treatment option for advanced HCC.

Biloma and liver abscess are well-known post TACE complications, with reported incidences of up to 3.3% and 2.5%, respectively. Additionally, dilatation of the bile duct and the formation of biloma often occur following RT. Therefore, the rate of biloma and liver abscess would likely increase after the sequential therapy, compared to either RT or TACE alone. However, we could not detect the above-mentioned complications in the cohort even when TACE was combined with RT. This result highlights the safety of performing TACE about local complications in patients who received liver RT earlier.

RT for the liver is reportedly associated with the risk of radiation-induced liver disease (RILD). The MLD of RT was found to be a significant predictor of short-term liver function impairment at 1 month following TACE. Thus, it is important to assess the MLD before TACE. In our study, short duration between RT and TACE (3 months) was a significant risk factor of liver deterioration and short-term mortality. It is presumed that TACE caused further liver damage when RILD was still ongoing. Thus, the short interval between RT and the following TACE may be considered a risk factor, highlighting the need to evaluate the interval between TACE and preceding RT.

This study had some limitations: the study design was retrospective, relatively small sample size, coexisting medical conditions and systemic therapy were not sufficiently assessed.

Conclusion

TACE following liver RT may be feasible. However, more attention should be paid to situations when there is an impairment of the pre-treatment liver function or after a high-dose RT. Moreover, it is advisable to delay TACE until RILD subside.

The candidate, having completed studies on the feasibility of transcatheter arterial chemoembolization following radiation therapy for hepatocellular carcinoma, with a specialty in combination therapy-induced complications and liver dysfunction, is hereby recognized as having qualified for the degree of Ph.D. (Medicine) .