# EFFECTS OF DIFFERENT TREATMENT OPTIONS ON THE LEVEL OF SERUM CYTOKINES IN PATIENTS WITH LIVER CANCER

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Liver cancer is a highly lethal tumor. Interaction between cancerous, stromal, immune cells and extracellular matrix proteins form immune suppressive tumor microenvironment. Local microenvironment and systemic immunosuppression allow tumor to escape immune surveillance [1].

Balance of pro- and anti-inflammatory cytokines, different expression of cytokines' receptors on responder cells and the activation state of surrounding cells not only regulate anti-tumoral response, but may have influence on transformations and malignancy of cells in the pathogenesis [2].

Several studies reported that an increased level of IL-10 characterizes different types of cancer. The positive correlation between serum IL-10 levels and tumor progression indicates a key role of IL-10 in the suppression of anti-tumor immune response and establishment of tumor environment. Its pro-tumorigenic effects depend on upregulation of Bcl-2 and downregulation of apoptosis [3].

TGF-β has a dual role in cell proliferation and cell death. Initially, it acts as a tumor suppressor, since it induces apoptosis and inhibits the growth of cells, but at later stages of tumor progression, it is tumor promoter - stimulates angiogenesis, induces T regulatory cells development, inhibits anti-tumor immune response and affects differentiation of epithelial and endothelial cells. It also reduces the amount of antigen presentation by dendritic cells [4]. TGF-β can promote self- renewal of cancer stem cells, or induces their differentiation. Increased levels of TGF-β have been shown to contribute to metastatic spread of tumor cells, via the epithelial/mesenchymal transition.

Pro-inflammatory cytokine, such as IL-17, also has dual effects on tumor immune surveillance (either promotes tumor growth via stimulating angiogenesis or inhibits tumor growth via stimulating cytotoxic T-cell response) [5]. IL-17 pro-tumorigenic role depends on its effect on fibroblasts and endothelial cells in the tumor microenvironment. IL-17 stimulates vascular endothelial cell migration, cord formation of vascular endothelial cells and regulates the production of a variety of pro-angiogenic factors. IL-17 induces vascular endothelial growth factor (VEGF), IL-1β, IL-6, PGE2, enhances ICAM-1 expression in fibroblasts and stimulates IL-8 production. All of these molecules are key factors in angiogenesis and tumor invasion. On the other hand, IL-17 stimulation can induce IL-12 production from macrophages [6]. Both IL-6 and IL-12 have been associated with tumor-specific cytotoxic T lymphocytes (CTL) induction.

IFN-γ is an important factor in the induction of CTL differentiation. IFN-g shows, cytotoxic and proapoptotic (By inducing of specific genes) effects [7], it upregulates MHC expression on tumor cells, inhibits angiogenesis (inhibition of tumor-derived angiogenesis is well-accepted mechanism to limit tumor growth), antagonizes suppression by tumor-derived TGF-β [8]. However, in contrast of these effects, the prolonged presence of IFN-γ promotes changes in tumor phenotype by survival of more aggressive clones of malignant cells, epigenomic or transcriptogenomic changes caused by IFN-γ in tumor cells favor escape from immune surveillance [9,10].

Surgery has always been considered as a gold standard for treatment of liver cancer, in recent years, patients with liver cancer are often managed by non-surgical locoregional treatment approaches, for example, radiofrequency thermal ablation (RFA). It represents minimally invasive treatment option and demonstrates good survival rate over the others with surgical resection when the tumor size is <3 cm [11-14]. RFA results in a higher rate of tumor necrosis (tumor size, number and sites are of importance). Additionally, many studies report that RFA provides adjuvant/"danger" signals to the immune cells, as a consequence stimulates CD4+ T helpers and causes a drastically increase of antigen-specific CD8+ T cells within the tumor microenvironment and tumor-draining lymph node [15-17].

We aimed to study changes in serum cytokines levels due to local disturbance of tumor microenvironment after radiofrequency thermal ablation procedure compare to liver resection in patients with primary and metastatic liver cancer.

**Material and methods.** We conducted a single center prospective pilot study at Tbilisi State Medical University hospital in accordance with the Declaration of Helsinki from 2014 to 2017. The study was approved by the Ethic Committee of the Tbilisi State Medical University and informed consent obtained from each recruited patient, with primary or secondary liver cancer. The primary endpoint of study was to assess the immunomodulatory changes in cytokines (IL-10, IFN-γ, IL-17, TGF-β) following RFA or liver resection in the liver cancer patients.

A total of 17 patients with primary (HCC and Cholangiocarcinoma) and secondary (metastasis from colorectal cancer) liver cancer were enrolled in this prospective study. Out of 17 patients, 7 were referred to RFA procedure and another 10 underwent surgical liver resection using non-RF based devices. All decisions regarding procedures were tabled by MDT (Multidisciplinary Team). 3 patients underwent anatomic segmental hepatectomy and non-anatomical resection was done in 7 patients. All liver resections were accomplished by using non-RF based liver resection devices. Healthy age-matched 14 volunteers without history of cancer, recent acute or chronic infectious disease, or autoimmune disease, were used as controls for the comparison.

The inclusion criteria for the RFA patients selection were as follows: a) extensive liver disease or medical co-morbidities associated with tumor vascular invasion and thromboses, b) fewer than three nodules without extrahepatic metastasis, c) largest tumor size of 3-4 cm in diameter, d) visualization of the nodule during the planning of RFA by ultrasonography (US). The exclusion criteria included treatment by chemotherapy or TACE, RFA or LR within previous one month.

*Radiofrequency thermal ablation (RFA).* An image guided RFA was performed by senior interventional radiologist at our centre. The tumor was localized and RF antenna introduced into the target tissue under US guidance. RF processing increases temperature into the target tissue up to $102^0$C leading to the irreversible damage by coagulative necrosis. Abdominal contrast computer tomography (CT) was performed to document completeness of the procedure. A peripheral blood samples were obtained one month before and after the procedure.

*Liver resection (LR).* Surgical resection, anatomic segmental hepatectomy and non-anatomical liver resection was carried out under the general anesthesia using an upper middle incision, using non-RF based liver resection devices.

Blood samples were collected from each patient before and after 1 and 3 months of treatment. The following serum cytokines: IL-10, IL-17, INF-γ, TGF-β were assayed by ELISA (ebiosciences, USA).

None of the patient had received chemotherapy or any other treatment a month before or 3 months after the LR and RFA procedure.

All data were entered into a Microsoft Excel™ database and analyzed using Graph Pad Prizm software. The Student's t-test was used to compare data between RFA and surgical resection group. Furthermore, both study groups were compared with healthy control subjects. *P* values less than 0.05 were considered as statistically significant.

**Results and discussion.** A total of 17 patients with liver cancer were included in the study. Patients' demographic characteristics of each group has been listed and compared in Table 1. The mean age of patients in RFA and LR group was 55.1±11.2 years and 58.6±8.1 years respectively (p>0.05). There were 3 women (43%) and 4 men (57%) in the RFA cohort whilst, 5 women (50%) and 5 (50%) men in the LR group. Along with that, we didn't observe any significant differences between groups regarding number of tumors, primary or secondary, tumor size, tumor stage, HBsAg, Anti-HCV positive.

The present study showed increased level of IL-10 in patients who underwent RFA procedure compare to healthy age-matched volunteers without history of cancer (p<0.05). 1 month after RFA procedure serum level of IL-10 declined (P<0.01) and was comparable with control. 3 months after RFA procedure serum level of IL-10 continued to reduce (p=0.03). In the patients before liver resection serum level of IL-10 was comparable with indices in healthy volunteers. 1 month after liver resection (LR) serum level of IL-10 increased (p<0.01) and continued to enhance at the point of 3 months after LR (P=0.006) (Fig. 1).

Serum levels of IL-17 were higher in patients, compare to control group and did not change 1 and 3 months after RFA and LR (p>0.05) (Fig. 2).

Serum levels of IFN-γ, were higher in RFA group compare to LR group. 1 and 3 months after treatment it showed decline approximately to control level (P>0.05) (Fig. 3).

Pre-procedural serum level of TGF-β was high, compare to healthy age-matched volunteers. It decreased 1 month after RFA and LR. Noteworthy, in our study at the point of 3 months after RFA procedure it continued to decrease, while at this point TGF-β remained the same in LR group (P>0.05) (Fig. 4).

Cytokines are the main mediators for the growth, invasion and metastasis of cancer. They are produced by cancer cells as well as immune and stromal cells in the affected area and are responsible for further uncontrolled proliferation of malignant cells, remodeling of tumor microenvironment, triggering of intrinsic inflammation, recruiting cells, angiogenesis and cancer cells spread [18].

Clinicopathological factors: higher AFP, tumor size, metastases, lower grade of differentiation are important predictors of the outcome of disease [19]. It is shown, that pre-treatment serum level of cytokines also widely varies in patients with liver cancer and highly determines the prognosis of diseases. Higher pre-therapy serum level of IL-17 and lower IL-10 level predicted poor prognosis (early recurrence of tumor) after surgery in patients with HCC. Other cytokines: IL-23, IL-8, IL-1b, IL-6, IL-1a and TNF-α were not associated with recurrence time of disease [20]. It was supposed, that IL-17 and IL-10 along with other factors form cancerogenic environment responsible for tumor recurrence.

As is consistent with the literature, our study showed that compared with the baseline serum cytokine levels (IFN-γ and TGF-β) there were no significant changes in serum levels of these markers one month after curative treatments (RFA and resection) [21].

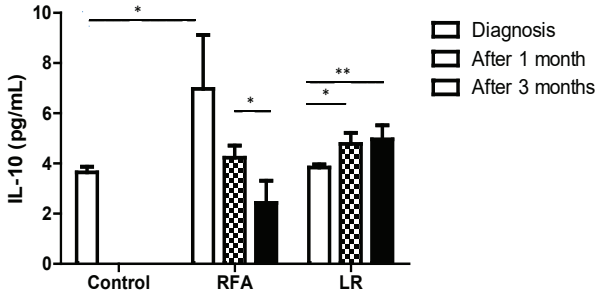


*Fig 1. Serum IL-10 levels in patients with liver cancer before and after 1 and 3 months of RFA and liver resection*
*LR group - diagnosis vs. after 1 month – P<0.01; Diagnosis vs. after 3 months- P=0.006; RFA group- diagnosis vs. after 1 month- P< 0.01; After 1 month vs. after 3 months- P=0.03*

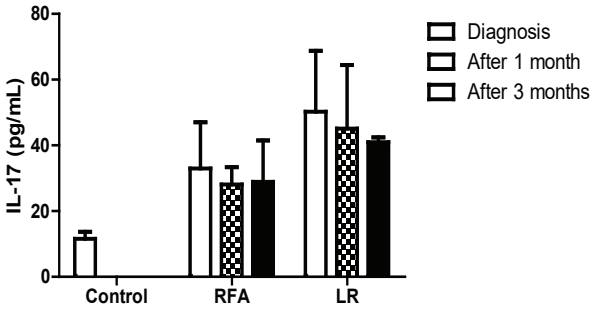


*Fig 2. Serum IL-17 levels in patients with liver cancer before and after 1 and 3 months of RFA and liver resection*

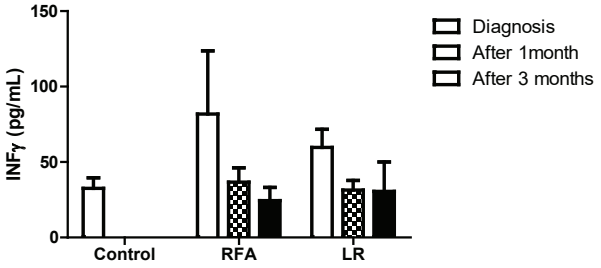


*Fig 3. Serum INFγ levels in patients with liver cancer before and after 1 and 3 months of RFA and Liver resection*

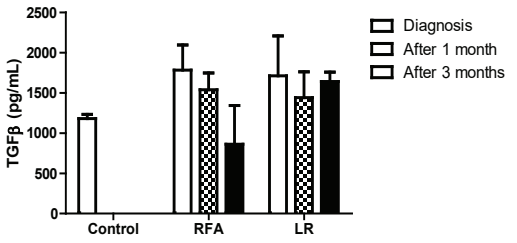


*Fig. 4. Serum TGFβ levels in patients with liver cancer before and after 1 and 3 months of RFA and Liver resection*

We showed that serum level of IFN-γ in patients had tendency to increase compared to healthy donors as it was observed by A. M. Attallah et al. [22] and in contrary by L. Ji et al. [23]. L. Ji reported that changes of IFN-γ under the influence of the RFA treatment was depended on the AFP level of patients with liver cancer: in patients with reduced AFP levels Th1 cytokines increased, whereas Th2 cytokines decreased after 1 month of treatment. However, in few patients with increased AFP level after RFA treatment IL-2, TNF-α, IFN-γ serum levels significantly declined and IL-4, IL-6 and IL-10 serum levels markedly enhanced ($p<0.05$).

Our study showed an enhanced level of TGF-β in patients with liver cancer in comparison with healthy donors, which insignificantly decreased by both treatment options. It continued to reduce at the point of 3 months after RFA therapy and remained unchanged in the LR group. The newest studies explained the dual role of TGF-β in liver cancer development [24]. This cytokine performs cytostatic and apoptotic function and is considered as tumor suppressor at early stages of tumor development. However, accumulation of suppressor cells: Tregs, MDSC and tumor cells by themselves produce high amount of TGF-β, which inhibits Th1, TCL, NK at advanced stage and promotes tumor escape from immune surveillance. TGF-β presents one of the key cytokines associated with angiogenesis and fibrogenesis. Some studies provided evidence about TGF-β inhibitors in patients with advanced HCC. Tendency of continuous reduction of TGF-β after RFA treatment in our study highlights the beneficial effect of such treatment.

Th-2 cells, B cells, tumor cells and macrophage produce one of the most important immunosuppressive mediator IL-10 - a potent inhibitor of pro-inflammatory cytokines (including IL-1β, TNF-α and IL-6). IL-10, together with TNF-a, autocrinally stimulates the expression of negative costimulatory molecule B7-H1(PDL-1) on macrophage surface - impairs $CD8^+$ T cell activity and supports tumor immune escape [25]. Our results revealed that, radiofrequency ablation and hepatic resection showed the opposite effects on serum IL-10 level in patients with liver cancer: RFA procedure significantly decreased serum level of IL-10, inconsistent with LR, which significantly increased this indicator.

We suppose that important differences in immune responses evoked after two different treatment approaches can be explained by the destruction of tumor microenvironment by RFA and healthy tissue injury during resection.

Local immune responses to surgery lead to systemic proinflammatory and immunosuppressive phases: production of a variety of cytokines leading to a general inflammation: stress, activation of the hypothalamic-pituitary-adrenal axis, release of steroids, such as cortisol, facilitates to the healing of injured tissues. Immunosuppressive phase avoids autoreactivity but on the other hand, it can inhibit antitumor Th1 immune response, provokes development of postoperative immune suppression and stimulates tumor cells growth.

Others and our previous studies reported that destruction of tumor microenvironment by RFA favors the increase of expression of heat shock proteins and release of a wide spectrum of tumor antigens from necrotic cells. Natural adjuvants loaded by antigens are easily uptaken by dendritic cells and effector specific antitumor CD4+ Th1 cells as well as CD8+ T cytotoxic cells are recruited to the tumor microenvironment [26]. We suppose, that Th1 cytokine milieu can establish antitumor environment and inhibits production of IL-10 by Th2, TAM and other cells. These events account for the immunotherapeutic effect of RFA.

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## SUMMARY

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Liver cancer is a highly lethal cancer, in which local tumor microenvironment and systemic immune suppression allow tumor to escape immune surveillance. Intervening in tumor microenvironment by locoregional treatment options can be beneficial for patients.

We aimed to study changes in serum cytokines levels due to local disturbance of tumor microenvironment after radiofrequency thermal ablation procedure compare to liver resection in patients with primary and metastatic liver cancer.

A total of 17 patients with primary (HCC and Cholangiocarcinoma) and secondary (metastatic) liver cancer were enrolled in this prospective study. Out of 17 patients, 7 were referred to RFA procedure and another 10 underwent surgical liver resection using non-RF based devices.

Blood samples were collected from each patient before and after 1 and 3 months of treatment. The following serum cytokines: IL-10, IL-17, INF-γ, TGF-β were assayed by ELISA (ebiosciences, USA).

RFA procedure unlike liver resection decreased serum level of IL-10 in patients with liver cancer. No significant changes in the level of the studied cytokines were revealed.

**Keywords:** proinflammatory, anti-inflammatory cytokines, IL-10, radiofrequency ablation, liver resection, liver cancer.

## РЕЗЮМЕ

### ВЛИЯНИЕ РАЗЛИЧНЫХ МЕТОДОВ ЛЕЧЕНИЯ НА УРОВЕНЬ СЫВОРОТОЧНЫХ ЦИТОКИНОВ У ПАЦИЕНТОВ С РАКОМ ПЕЧЕНИ

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Рак печени в большинстве случаев завершается летальным исходом. Воздействие местного микроокружения опухоли на иммунную систему позволяет опухоли избежать иммунологического надзора. Следовательно, разрушение микросреды опухоли местными методами лечения может оказаться эффективным для пациентов.

Целью исследования явилось изучение изменений уровня цитокинов, вызванных деструкцией опухолевой ткани в результате применения современного малоинвазивного метода радиочастотной термальной абляции и после резекции печени, у пациентов с первичным и метастатическим раком печени.

В проспективное исследование включены 17 пациентов с первичным (гепатоцеллюлярная карцинома и холангиокарцинома) и вторичным (метастатическим) раком печени. 7 пациентов из 17 подверглись радиочастотной термальной абляции (РЧА), 10 пациентам проведена резекция печени.

Забор крови проводили до лечения и спустя 1 и 3 месяца после лечения. Для измерения концентрации цитокинов (IL-10, IL-17, INF-γ, TGF-β) в сыворотке крови использовали метод иммуноферментного анализа - ELISA (Ebiosciences, США).

РЧА, в отличие от резекции печени, выявила снижение уровня IL-10 у пациентов с раком печени. Существенных изменений в уровнях остальных исследованных цитокинов не выявлено.

რეზიუმე

მკურნალობის სხვადასხვა მეთოდის გავლენა ღვიძლის კიბოთი დაავადებული პაციენტების შრატში ციტოკინების დონეზე

ნ. ქიქოძე, მ. იობაძე, ი. ფანცულაია, მ. მიზანდარი, ნ. ჯანიკაშვილი, თ. ჩიქოვანი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

ღვიძლის კიბო, ძირითადად, ლეტალური გამოსავლით სრულდება. სიმსივნის ლოკალური მიკროგარემოს ზემოქმედება იმუნურ სისტემაზე საშუალებას აძლევს სიმსივნეს თავი დააღწიოს იმუნოლოგიურ ზედამხედველობას. ამიტომ, სიმსივნის მიკროგარემოს დესტრუქცია, მკურნალობის ლოკალური მეთოდების გამოყენებით, შეიძლება სასარგებლო იყოს პაციენტისთვის.

კვლევის მიზანს წარმოადგენდა ღვიძლის კიბოთი დაავადებული პაციენტების მკურნალობის ორი განსხვავებული სტრატეგიის - რადიოსიხშირული თერმული აბლაციისა და ღვიძლის რეზექციის გავლენის შესწავლა პაციენტთა პერიფერიულ სისხლში ციტოკინების დონეზე.

პროსპექტიულ კვლევაში ჩართული იყო ღვიძლის პირველადი (ჰეპატოცელური კიბო და ქოლანგიოკარცინომა) და მეორადი (მეტასტაზური) კიბოთი დაავადებული 17 პაციენტი, მათგან 7-ს ჩაუტარდა რადიოსიხშირული თერმული აბლაცია (რსა), ხოლო დანარჩენ 10 პაციენტს - ღვიძლის რეზექცია.

თითოეული პაციენტისაგან სისხლის ნიმუშის აღება ხდებოდა მკურნალობამდე და მკურნალობის დაწყებიდან 1 და 3 თვის შემდეგ. პერიფერიული სისხლის შრატში ციტოკინების - IL-10, IL-17, INF-γ, TGF-β, განსაზღვრისთვის გამოყენებული იყო იმუნოფერმენტული ანალიზის მეთოდი ELISA (Ebiosciences, აშშ).

რსა-ის გამოყენებამ ღვიძლის კიბოთი დაავადებულ პაციენტებში, ღვიძლის რეზექციისაგან განსხვავებით, გამოიწვია შრატში IL-10–ის შემცირება. სხვა გამოკვლეული ციტოკინების დონის მნიშვნელოვანი ცვლილება არ გამოვლენილა.

## СРАВНЕНИЕ РЕЗУЛЬТАТОВ ВОССТАНОВЛЕНИЯ ПОВРЕЖДЕНИЙ АКРОМИАЛЬНО-КЛЮЧИЧНОГО СОЧЛЕНЕНИЯ КРЮЧКОВИДНОЙ ПЛАСТИНОЙ И ПУГОВЧАТОЙ ФИКСАЦИЕЙ TIGHTROPE

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Повреждение акромиально-ключичного сочленения - частая травма в области плеча, относящаяся к спортивной медицине и ортопедии [1,2]. Количество таких повреждений значительно увеличилось в результате роста объема дорожно-транспортных происшествий и вовлеченности в любительский спорт. Выделяются 6 степеней повреждения акромиально-ключичного сочленения в классификации по Rockwood [2,3]. Оперативное лечение показано при степенях повреждений III-VI по Rockwood. Однако, лечение III степени повреждения по Rockwood в научном мире носит дискуссионный характер, так как одни авторы говорят о необходимости консервативного лечения данного повреждения, другие склоняются к оперативному. При этом все авторы сходятся в одном, что оперативное лечение рекомендуется молодым пациентам, спортсменам, лицам, занимающимся физическим трудом. Оперативное лечение при свежих повреждениях акромиально-ключичного сочленения приводит к лучшим результатам [3-7].

Лечение акромиально-ключичного повреждения можно выполнять различными оперативными техниками. Обычно используют метод с установкой крючковидной пластины или артроскопическую технику TightRope, при применении которых добиваются хороших клинических результатов.

Установка крючковидной пластины может повлечь за собой некоторые проблемы, такие как акромиальный остеолиз, миграция металлофиксаторов, тендинит [8]. Помимо этого, после установки пластины пациенты часто испытывают боль в области сухожилия надостной мышцы оперируемого плеча и ограничение движения в нем. С учетом совокупности вышеотраженных возможных осложнений при установке данной металлоконструкции рекомендуется удалять крючковидную пластину по истечении определенного времени [9].

В качестве альтернативы существует метод артроскопической техники с использованием пуговчатого фиксатора (TightRope). У данного метода есть преимущества в виде малотравматичности и анатомичности при восстановлении нормального положения сустава, что невозможно при установке крючковидной пластины. При использовании данного метода нет необходимости удалять фиксатор [10].

Целью исследования явилось сравнение двух представленных методов при лечении акромиально-ключичного сочленения с установкой крючковидной пластины и при помощи пуговчатой фиксации TightRope.

**Материал и методы.** В период с 2015 по 2019 гг. 60 пациентам проведено оперативное лечение свежих повреждений акромиально-ключичного сочленения III–VI типа по Rockwood. Согласно оперативным методам, пациенты разделены на две группы пациенты первой группы (n=30) прооперированы с использованием крючковидной пластины, второй группы (n=30) – с применением техники TightRope. Соотношение пациентов по гендерному признаку - 48 (80%) мужчин и 12 (20%) женщин. Возраст пациентов варьировал в пределах от 23 до 54 лет, средний возраст - 35.2±8.2 г.

Все пациенты получали лечение в течение 3 недель с момента травмы. 30 пациентам первой группы фиксация вы-