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Transplantation in oncology: the future of a multidisciplinary approach

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On February 7, 2019, a one-day Consensus Conference of the International Liver Transplantation Society was held to discuss oncology issues. Representatives of world's leading clinics gathered in Rotterdam (Netherlands). The presentations made on that day covered the following topics: hepatocellular cancer, bile duct cancer, immunotherapy and its place in the treatment of liver tumors, the possibility of liver transplantation in patients with metastatic liver disease, world trends in pediatric oncohepatology. A *separate session in the working groups was allocated to discuss the most actual topics.*

The Conference identified the main global trends and the most crucial issues in the field of liver transplantation in patients with oncological diagnosis. It

is likely that these presentations will "set the tone" for the large Transplantation Congress in Toronto in May 2019.

Keywords: liver transplantation, hepatocellular cancer, alpha-fetoprotein, immunotherapy, cholangiocarcinoma, Klatskin tumor, liver metastatic lesion, hepatoblastoma

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AFP, alpha fetoprotein

BCLC, Barcelona Clinic Liver Cancer system

CCA, cholangiocarcinoma

CT, computed tomography

DCP, Decarboxylated Prothrombin (Des-gamma-Carboxy-Prothrombin)

FDG, fluorodeoxyglucose

HCC, hepatocellular cancer

NASH, nonalcoholic steatohepatitis

NLR, neutrophil-lymfocyte ratio

PET, positron emission tomography

RFA, Radiofrequency Ablation

TACE, Transarterial Chemoembolization

Hepatocellular cancer

On February 7, 2019, the ILTS Conference *Transplant Oncology - the Future of Multidisciplinary Management* was held in Rotterdam (the Netherlands) that discussed oncology issues in hepatology. The Meeting lasted one day and was very intense. Central topics of the discussion were the treatment of hepatocellular cancer (HCC) and various aspects of liver transplantation related to cancer.

At the beginning of the Meeting, Mr. J.Roberts from the University of San Francisco (California, USA) listed the most relevant issues for discussion. The cornerstone of his presentation was the optimal selection criteria for those patients who have a chance of a long recurrence-free period after liver transplantation. There have been many attempts to formalize such an approach; the traditionally proposed algorithms are called "advanced" criteria (relative to Milan criteria), and also traditionally, following Milan and San Francisco, they are given the names of the cities by the centers where they were developed. Contemporary experts propose, along with the size of the liver tumor, to include the biological markers of the tumour "aggressiveness", primarily alpha-fetoprotein (AFP). At the same time, the cut-off threshold for the AFP level has not been established: options of 20, 100, 200, 400, 1000 ng/ml have been proposed (and argued). Other criteria have also been proposed: PIVKA II level, response to therapy, degree of tumor differentiation, dynamics of AFP decrease after the treatment. Unfortunately, PIVKA II decarboxylated prothrombin (DCP) is not routinely determined in Russia.

In HCC epidemiology, two aspects are worth noting. First, using the available HCV therapy with direct-acting drugs it was possible to reduce the risk of developing cancer in patients with liver cirrhosis. The second

important advantage of currently available antiviral therapy is the possibility of reducing the liver failure. M.Berenguer from the University of Valencia (Spain) presented WHO statistics for 2016 [1]: about 71,000,000 people are infected with hepatitis C worldwide, every fifth of whom dies from HCC. Russia immediately fell into two sad ratings: as one of the 7 countries where half of the world hepatitis C patients live, and as one of the 5 countries where the incidence is above 3% (alongside with Mongolia, Egypt, Georgia, and Pakistan). On a population scale, HCV treatment leads to a change in the waiting list structure: in recent years, fewer HCV-infected patients have been included in it, they are more stable, so the mortality in the List has reduced, while the percentage of patients withdrawn from the List due to an improved liver function has more than doubled (E. Saez-Gonzalez, 2017 [2]). The presentation made by P.Burra from the University of Padua (Italy) covered the epidemiology of fatty liver disease, in particular, non-alcoholic steatohepatitis (NASH) which incidence among the population is increasing every year. This tendency has various negative consequences: on the one hand, it leads to an increased HCC occurrence against the developed cirrhosis in the NASH outcome, and on the other hand, it results in a deterioration of donor organ quality. All hopes in this matter are put on the technologies of hepatic graft extracorporal perfusion.

In most cases, HCC occurs in the presence of liver cirrhosis, and these patients often need liver transplantation. It may not always be possible and depends on the balance between the intended benefits (upcoming life expectancy) and the risk of surgical complications associated with the operation, the increased rates of cardiovascular and general oncological risks associated with administered immunosuppressive therapy in recipients.

The choice of the optimal treatment strategy for each individual patient should be justified. In the current Guidelines of the European Association for the Study of the Liver (2018), the Barcelona Clinic Liver Cancer System (BCLC) is preferred, with the advantage of being able to offer one of several therapeutic tactics depending on the severity of the patient's condition and the tumour staging. But even such a "stock" of options may be insufficient in practice, for example, in relation to the patients who have undergone neoadjuvant therapy. In addition, it does not take into account the biological markers of HCC. The BCLC algorithm compensates for the lack of flexibility, providing the doctor with the right to apply the strategies originally designed for milder or more severe cases, with regard to the individual characteristics of the patient. Prof. V.Mazzaferro considered such tactics preferential as compared to others having more stringent limitations. However, a deterministic algorithm seems to be optimal, which would take into account a greater number of patient parameters and offer an individual treatment strategy, without leaving such a subjective component as the opinion of an individual specialist.

The tendency to use the biological parameters of the tumor for the selection of the optimal treatment method affected not only the surgical concepts, but also greatly influenced the search for systemic therapy. In 2014, J.M.Llovet published an article in which he analyzed the existing arsenal of drugs and concluded that sorafenib was the only agent with a proven efficacy [3]. To date, on the one hand, the mechanisms of resistance to sorafenib have been investigated, and on the other hand, alternatives to this drug are being actively developed. Prof. R.M.Ghobrial from Weil Cornwall Medical College (New York, USA) presented an overview of new trends in systemic therapy for HCC, and this list is not limited to checkpoint

inhibitors. The cited article by I.Melero from Nature Review [4] has listed a dozen and a half of promising agents for immunotherapy in HCC (Table 1). It is worth noting that 6 of them formally refer to vaccines.

R.M.Ghobrial also cited a table from the ClinicalTrials.gov research database with a long list of medicinal agents undergoing Phase III clinical trials (Table 2).

Table 1. The immunotherapeutic agents being under development and having proved effective

Vaccines • Vaccines based on dendritic cells • Vaccines based on autologous granulocyte-macrophage colony-stimulating factor (GM-CSF) • Virus Vector Vaccines • mRNA-based vaccines • Multipeptide vaccines • Local virotherapy
Targets of modulatory monoclonal antibodies • Cytotoxic T lymphocyte antigen-4 (CTLA-4) • Programmed cell death protein-1 (PD-1) • Programmed death-ligand 1 (PD-L1) • CD137 • OX40 • Lymphocyte-activation gene 3 (LAG3) • T-cell immunoglobulin and mucin-3 domain (TIM3) • Glucocorticoid-induced tumour necrosis factor receptor (GITR) • CD27
Adaptive T-cell therapy • Tumor-infiltrating lymphocytes • Chimeric antigen receptors (CARs) • CAR-transduced T-lymphocytes

Table 2. Groups of the biological agents promising for hepatocellular cancer treatment

Phase III trials	**Antiangiogenic agents:** VEGF, VEGFR, VEGFR2, VEGFR2 / 3, c-KIT, PDGFR, endoglin; **Targeted agents:** MET, MET / tubulin, retinoic acid receptors, arginine deiminase, angiopoietin-1 receptor; **Epigenetic modulators:** DNMT, miR494, histone deacetylase, miR-34, EGFR/HER2; **Cell cycle inhibitors and antiproliferative agents:** mTOR, TGF-bR1, MET, FGFR1-4, FGER3, aurora kinase, EGFR, AKT, MEK, RAF, PLK1 **Pro-apoptotic and DNA damaging agents:** TRAIL-R1, PARP, BCL2, BCLX; **Immune modulators:** STAT3, CTLA-4, PD-1, protein S100A9; **Others:** adenosine A3 receptors, glypican-3, phospholipids of cancer stem cells, proteasomes;
Phases I – II trials	Signal pathways TGF-b, FGF19/FGFR4, RAS
New mechanisms	DNA and miRNA targeting agents

A special attention in almost every report was given to checkpoint blockers. Prof. H.Metselaar successfully compared this interest with the curiosity towards new members in the team. Prof. R.M.Ghobrial cited data from the CheckMate040 and KeyNote-224 studies, which showed impressive results of nivolumab and pembrolizumab as second-line drugs for the HCC treatment. The cited review by M.Kudo [5] listed the ongoing studies (Table 3). Prof. B.Sangro from the University of Navarre (Spain) cited clinical cases of successful treatment of HCC generalized forms.

Table 3. Checkpoint inhibitors; Trials conducted in 2018 (Kudo data)

Agent	Trial name	Number in the ClinicalTrials.gov database	Phase	Number of patients	Line of therapy	Design	Purpose of the Trial
Nivolumab / Ipilimumab	CheckMate 040	NCT01658878	I / II	42	1–2	1st cohort: dose increase	Dose limiting toxicity, median survival time

	CheckMate 040	NCT01658878	I/II	214	1 – 2	2nd cohort: expansion of indications to the maximum dose	Overall response rate
	CheckMate 040	NCT01658878	I / II	200	one	3rd cohort: nivoluumab vs sorafenib	Overall response rate
	CheckMate 040	NCT01658878	I / II	120	2	4th cohort: nivolumab + ipilimumab	Safety, tolerability
	CheckMate 040	NCT01658878	I / II	–	1	5th cohort: Child B Nivolumab	Overall response rate
	CheckMate 040	NCT01658878	I / II	–	1	6th cohort: nivolumab + cabozantinib	Overall response rate
	CheckMate 040	NCT01658878	I / II	–	1	7th cohort: nivolumab + ipilimumab + cabozantinib	Overall response rate
	CheckMate 459	NCT02576509	III	726	1	Nivolumab vs sorafenib	Time to progression, overall survival
Pembrolizumab	KEYNOTE -224	NCT02702414	II	100	2	Pembrolizumab (1 arm)	Overall response rate
	KETNOTE-240	NCT02702401	III	408	2	Pembrolizumab vs placebo	Survival without progression, overall survival
Durvalumab / Termelimumab	–	NCT02519348	II	144	1 – 2	Durvalumab (Arm A) Termelimumab (Arm B) Durvalumab + Termelimumab (Arm C)	Safety, tolerability
Durvalumab + Termelimumab	–	NCT028211754	I / II	–	TACE / RFA	1st group	Safety, tolerability
Durvalumab + Termimumab vs Sorafenib	–	NCT03298451	III	–	1	Durvalumab + Termimumab vs Sorafenib	Overall survival rate
MSBoo11359C (PD-L1 Ab + TGFB Trap)	–	NCT02699515	I	–	1	1st group	Safety, tolerability
PDR001 +	–	NCT02795429	I/II	–	1-2	PDR001 +	Safety,

INC280						INC280	overall survival
LY3300054 + LY3321367	-	NCT03099109	I/II	-	1-2	LY3300054 + LY3321367	Safety, overall survival

An open question remains as to the search for the optimal combination of surgical and therapeutic techniques - chemotherapy and immunotherapy courses, the procedures of transarterial chemoembolization, radiofrequency ablation, remote radiation therapy, resection, and, of course, transplantation. Each of these methods has its own limitations and contraindications for use in individual patients. In addition, not all centers have an access to all the methods. The Conference did not set itself the task of summing up the common denominator in this matter; nevertheless, presentations on the "Western" and "Eastern" approaches were singled out in a separate section.

The position of the conditional West was represented by Dr. F.Yao from the University of San Francisco. He paid attention to making the HCC diagnosis using contrast-enhanced ultrasound routinely used in the United States. This method allows the HCC differentiation due to the characteristic symptom of "washing out" and in combination with a diagnostic algorithm approved by the American Association for the Study of Liver Diseases in 2011, which gives good results [6]. From his point of view, the efficacy of the liver resection on oncologic indications in the pre-transplantation period is an important predictor for the prognosis of transplantation. If we correctly approach the patient selection, the survival of patients initially satisfying the Milanese criteria and of those who underwent down-stage therapy would be the same [7]. The correlation between a high pre-operative AFP level and the worst survival rate after transplantation in comparable tumor sizes was shown in the studies of N.Metha [8] and C.Duvoux [9]. In France, in

accordance with the national guidelines, the level of AFP has been entered into the Risk Estimation of Tumor Recurrence after Transplant Score to predict HCC recurrence risk in the graft. In addition, doctors try to take into account the degree of HCC differentiation, they even suggest that any node larger than 1 cm should be considered an indication for a diagnostic biopsy. The Western world is actively looking for new risk estimation parameters; the University of Toronto (Canada) published a paper in 2016, where the location of nodes (intraparenchymal, without invasion into large vessels), the absence of emaciation signs in cancer and a high or moderate degree of the tumor differentiation [10] were included in the list of patient selection criteria for transplantation. At the same time, biopsy has not been generally accepted, since it can theoretically provoke microvascular invasion; in 8% of cases, poorly differentiated HCC is not identified at biopsy examination. In the Hameed retrospective study, among the patients who met the Milanese criteria, a 5-year survival of recipients with baseline AFP lower 100 ng/mL was 80%, and only 52% in the recipients with AFP over 1000 ng/mL [11]. Currently, under the US National Protocol, all candidates for transplantation with AFP above 1000 ng/mL are considered as having the indication to a down-stage therapy aimed at reducing AFP to the level below 500 ng/mL. The patients whose AFP levels have not decreased, are denied from liver transplantation.

“A look from the East”, a review of data from Turkey to Japan, was presented by Dr. Avi Soin from the Medanta Clinic in India and more likely complemented what was said by the Western colleagues rather than conflicting: the same trend towards biomarkers, selective expansion of the Milanese criteria. In geographic Asia, the positron emission tomography (PET) with fluorodeoxyglucose (FDG) is more commonly used; besides

AFP, the DCP assessment and MoRAL score are used as reliable tools [12]. Large centers in different countries develop their criteria and in varying degrees are guided by Western colleagues. A specific feature of the East is a large proportion of transplants from living donors and some of the centers mentioned in the presentation (for example, Florence Nightingale Clinic (Istanbul, Turkey, or Ankara University Hospital) use broader criteria for candidates for such operations. The multicenter study in Japan looks impressive demonstrating a 5-year recurrence risk of 8% in a cohort of patients "in Milan" or "outside Milan, but with AFP of lower 115 μg/L, and no metastases according to PET". For comparison, among the patients who did not meet those criteria, the recurrence risk was 53% within 5 years after transplantation [13].

There is no consensus among experts as for the treatment of the HCC patients in the waiting list for liver transplantation. There are countries where people stay in the waiting list for a long time, and it would be logical to try treating HCC at this time. In this case, patient's response to therapy may also be considered as a factor in predicting the recurrence in the graft. During the Meeting, this idea was first expressed by V.Mazzaferro, who formulated a general opinion on this issue in many respects. In general, experts proposed a follow-up period from 3 to 6 months for evaluating the response to therapy. An efficacy comparison was made between the various criteria and classifications for predicting the outcome of liver transplantation, the comparison data are summarized in Table 4 and 5.

Table 4. Criteria for the selection of hepatocellular cancer patients for transplantation

Title	Morphological criteria	Biological criteria	Survival data
Milan	1 node <5 cm; 3 nodes <3 cm each	No	4 years - 85%
San Francisco	1 nod <6.5 cm; 2-3 nodes <4.5 cm each; Sum of node diameters <8 cm	No	5 years - 72.4%
Pamplona	1 node <6 cm; 2-3 nodes <5 cm each	No	5 years - 79%
Edmonton	1 node <7.5 cm; Multiple nodes <5 cm each	No	4 years - 82.9%; 4 years without relapse - 76.8%
Dallas	1 node <6 cm ; 2–4 nodes <5 cm each	No	5 years without relapse - 63%
Valencia	1-3 nodes <5 cm each ; Sum of diameters <10 cm	-	5 years - 67%
Up-to-seven	Diameter of the largest node + their number <7, in the absence of microvascular invasion	No	5 years - 71%
Hangzhou	Sum of diameters <8 cm ; Sum over 8 <+ GI – II differentiation	With a diameter of more than 8, AFP <400 ng/mL	5 years - 70.7%; 5 years without relapse - 62.4%
Rome	Sum of diameters <8 cm	AFP <400 ng/mL	5 years - 74.4%
Warsaw	UCSF or Up-to-Seven	AFP <100 ng/mL	5 years - 100%
Geneva	Total tumor volume <115 cm^3	AFP <400 ng/mL	4 years - 78%
Toronto	Milan criteria	AFP <500 ng/mLl	5 years - 78%
	Any size / number of nodes; Differentiation G1–2; No cancer-associated symptoms	AFP <500 ng/mL	5 years - 68%
Metroticket 2.0	Up-to-seven Up-to-five Up-to-four	AFP <200 ng/mL AFP <400 ng/mL AFP <500 ng/mL	5 years - 75%
US National Criteria	Milanese criteria or the patients after a down-stage therapy who met Milanese criteria	With AFP> 1000 ng/mL, a reduction to <500 ng/mL is indicated.	-
TTV + AFP	TTV <115 cm^3	AFP <400 ng/mL	-
pre-MoRAL	Maximum node size	AFP, NLR	5 years depending on the risk group: low - 95%, below average - 75%, above average - 48%, high - 17%
Tokyo (rule 5–	No more than 5 nodes, no more than 5 cm	-	5-year relapse-free survival

5)			rate - 94%
Kyoto	No more than 10 nodes, totally no more than 5 cm	DCP <400	Over 5 years, overall survival 80–87%, tumor recurrence 5–7%
Asan	Not more than 6 nodes, diameter less than 5 cm, without macrovascular invasion	-	5-year survival rate - 76%
Kyushu	Any number of nodes less than 5 cm in diameter	DCP <300	5-year survival rate - 82%
Turkey	Intraparenchymatous nodes without portal vein involvement	-	5-year survival rate - 56%
Samsung	Not more than 7 nodes, not more than 6 cm	AFP <1000 ng/mL	5-year survival rate - 90%
Medanta	Intraparenchymal nodes without the involvement of large vessels	-	5-year survival rate - 65%

Table 5. Prognostic scores for liver transplantation outcome in hepatocellular cancer

Scores	When applicable	Parameters	Formula and Range of Values	Parameter for prognosis
Moral	Before OLT and intraoperatively	NLR> 5 (6 b), AFP> 200 (4 points), maximum diameter> 3 cm (3 points), G4 differentiation (6 points), vascular invasion (2 points), maximum diameter> 3 cm (3 points), number of nodes> 3 (2 points)	0–2 low risk 3–6 moderate risk 7–10 high risk > 10 very high risk	Disease-free survival
HALT-HCC	Before OLT	Tumour burden score (TBS= number of nodes + maximum diameter), AFP, MELD-Na	1.27 * OH + 1.85 * lnAFP + 0.26 * MELD-Na	Survival
French Model	-	The number of nodes is 1-3 (0 points), 4 or more (1 point); Maximum diameter is less than 3 cm (0 points), 3–6 cm (1 point), 6 or more (4 points); AFP <100 (0 points), 100–1000 (2 points),> 1000 (3 points)	0–2 low risk > 2 high risk	Disease-free survival
Metroticket 2.0	Before OLT	Number of nodes, maximum diameter, AFP	http://www.hcc-olt-metroticket.org/	Overall survival rate
Edmondson	After OLT	Node size, degree of differentiation	0.382 × (size in cm) + 1.613 × (with G3–4) The calculated parameter threshold 2.3	Overall survival after 1, 3, 5 years - 87, 74, 68% with relapse-free survival - 94, 81, 78%

Note: OLT, orthotopic liver transplantation.

The discussion of ethical issues is not the most expected topic at a clinical conference, but in fact it is very important. The “waiting list” is impossible without a formalized algorithm of the recipient selection, which means that it is necessary to adopt some moral guidelines, and it would better that they were universal throughout the medical community. Speaking of transplants from a posthumous donor, Prof. V.Mazzaferro noted that the EASL recommendations of 2018 [14] were missing significant ethical issues. From his point of view, it is necessary to find a balance between benefits for a particular patient and benefits for the society as a whole. An improvement in the HCC prognosis was observed in all patients from the waiting list who underwent transplantation. It is worth noting that among patients with HCC, there are people who even without transplantation have a relatively good prediction of survival (1 node of 2–3 cm that was excised or otherwise destroyed, AFP lower 20 μg/L, (according to Metha, 2013). The question was raised about the feasibility of placing these patients on the waiting list on a general basis, without the preferences common to HCC patients. At the same time, there are patients with a very high risk of recurrence and a relatively low prognosis for survival after liver transplantation. In the audience opinion, the ideal algorithm for the allocation of donor organs should take these factors into account, but its development is still a matter of the future.

The issues of life-long donation also affect ethical aspects. Today, most of these transplantations are performed in the geographical East, but gradually, in the western centers, the percentage of transplantations from living donors is increasing. Studies have confirmed that the overall recipient survival and the timing of tumor recurrence do not depend on the donor

type. And though the ethical issue of using live organ donation has been generally resolved thanks to a detailed survey and providing proper information, however, the question of choosing a cohort of HCC patients for whom transplantation from a living donor would be acceptable is still open. Do we have the right to take a liver fragment from a live donor, knowing that with a high probability the recipient will return the HCC within a few years? On the other hand, do we have the right to refuse assistance if the donor, despite these risks, wants to help his/her loved one? No final solution to this dilemma had been found by the end of the event, but the working group agreed that the criteria for inclusion in the transplantation program should be different for those who entered the waiting list for liver transplant from a post-mortem donor and those who have a live donor. As a rule, more expanded criteria are used for indications to transplantation from a living donor than for the inclusion in the waiting list.

A series of presentation on the management of liver recipients was opened by Dr. S.Bhoori, a representative of V.Mazzaferro's group from Milan. The topic was divided into three categories 1) the risk reduction at the preoperative stage; the data and conclusions were consistent with the general provisions expressed by other scientists; 2) the correction of postoperative management in order to minimize the risk of recurrence; 3) the treatment of HCC metastases in the graft. The last two aspects were brought up for discussion by a separate working group. Despite the heated debate, the wording proposed for consensus remained very prudent. Liver recipients were not recommended the immunosuppression protocols including cyclosporine; generally, minimizing the dose of calcineurin inhibitors was considered desirable. As for mTOR inhibitors, the concept of their use for the prevention of HCC relapse was based on laboratory studies and currently

it has not been confirmed by reliable clinical data [15]. At the same time, the use of these drugs allows the dose of calcineurin inhibitors to be reduced, which is in line with the cancer prevention goals. The data from a successful pilot study on the prophylactic administration of sorafenib in recipients with a high risk of recurrence were presented. However, since the study was small, such a scheme was not included in the final recommendations. S.Bhoori divided all HCC relapses into two categories: early and late. A number of researchers, including Prof. J.Lerut from the University of Saint-Luc in Brussels (Belgium), did not support such classification, considering that “late recurrences” are de novo tumors and require a different approach. A general approach to such patients should be "resect it if it is within your power". Speaking of a systemic therapy, at the moment sorafenib remains the first-line drug for patients with recurrent HCC in the graft.

In fact, immunotherapy of HCC in liver recipients remains an unexplored issue. In literature, there are 13 descriptions (Table 6) of the immunotherapy use (nivoluumab, ipilimumab, and pembrolizumab) in liver recipients, in 7 cases for the HCC progression. Four patients developed a severe rejection that ended up fatally. Currently experts agree on the possibility of using immunotherapy after liver transplantation only within the framework of clinical trials, and with preliminary administration of glucocorticosteroids.

Table 6. The reported cases of liver recipient treatments with checkpoint inhibitors from literature

#	Age	Type of cancer	Time from surgery to immunotherapy	Pharmacological agent	Immunosuppression	Number of dosing	Rejection?	Response to treatment	Authors
1	70	HCC	8 years	Pembrolizumab	Tacrolimus	8	No	Progression	Varkaris A., 2017
2	67	Melanoma	8 years	Ipilimumab	Sirolimus	20	No	Stabilization	Morales R., 2015
3	54	Non-small cell lung cancer	13 years	Nivolumab	Glucocorticosteroids + tacrolimus + everolimus	3	No	Progression	Biondani P., 2017
4	20	HCC	3 years	Nivolumab	Sirolimus	2	Yes	Unknown	Friend B., 2017
5	14	HCC	3 years	Nivolumab	Tacrolimus	1	Yes	Unknown	Friend B., 2017
6	41	HCC	2 years	Nivolumab	Tacrolimus	15	No	Progression	De Toni E., 2017
7	62	Melanoma	6 years	1) Ipilimumab; 2) Pembrolizumab	Sirolimus, mycophenolate mofetil	1) 8; 2) 25	1) No 2) No	1) Progression; 2) Partial response	Kuo J., 2017
8	67	Ocular melanoma	18 months	Ipilimumab	Prednisolone 10 mg	1	Yes	Progression	Dueland S., 2018
9	57	HCC	3.5 years	Pembrolizumab, Sorafenib	Tacrolimus, mofetil mycophenolate, prednisolone	14	No	Complete radiological response	Rammohan A., 2017
10	59	Melanoma	8 years	Ipilimumab	Tacrolimus	4	No	Progression	Ranganath H., 2015
11	35	Melanoma	20 years	Pembrolizumab	Tacrolimus	2	No	Complete radiological response	Schvartsman G., 2017
12	53	HCC	3 years	Nivolumab	Everolimus	1	Yes	Unknown	Gassmann et al., 2018
13	51	HCC	8 months	Nivolumab	Tacrolimus, everolimus	11	No	Progression	Bogomolov et al., 2019

Tumors of the bile ducts

The second most important topic was the bile duct tumors. Over the recent forty years, the incidence of cholangiocarcinoma (CCA) has changed its structure. Using the USA as an example, it was shown that with a stable incidence of extrahepatic tumors (about 1:100,000 people/year), the rates of diagnosing intrahepatic CCAs increased threefold [16]. Dr. M.Jalve (University of Texas, USA) was prone to explain this primarily by the improvements in diagnostic techniques, but the proven fact was the increase in the rates of CCA in patients with metabolic syndrome [17]. Resection is considered the preferred treatment option at the first stage, but it is not always feasible due to the tumour size or its hard-to-reach location, the presence of cirrhosis or distant metastases in a patient.

The guidelines of 2014 for the diagnosis and treatment of intrahepatic CCA [18] stated that only 30-40% of the cases were eligible for resection, and a 5-year survival after radical resection was no more than 40%, while the recurrence rate for that time period reached 60% to 70 %. Such patients are not recommended for liver transplantation due to a high incidence of relapses, however, these recommendations have been based on a very modest global clinical experience and have not stratified patients by the presence of cirrhosis. Dr. G.Sapisochin (Toronto, Canada) presented data from a retrospective study of 29 liver recipients, in whose explants CCA of less than 2 cm were found [19]. A 5-year survival of those patients was 73%. The survival prognosis of inoperable patients with CCA remains quite pessimistic.

The reviews and studies of 2014 cited by Dr. M.Jalve demonstrated a very low efficacy of chemotherapy for disseminated tumors, with overall

survival of no more than 14 months, regardless of the treatment scheme [20, 21]. The results of Tao study in patients with inoperable intrahepatic CCA were more optimistic: after a combination treatment of chemotherapy + radiation therapy, a 3-year survival was 78% [22]. As in many other areas, the molecular genetic approach has shown new ways of potential effects on bile duct tumors. The presentation of M.Jalve showed the differences between intra- and extrahepatic CCA and gallbladder cancer at the genetic level [23] (Table 7). Over the recent 10 years, the research has been conducted on investigating some of the mechanisms described. There are the inhibitors of isocitrate dehydrogenase (IDH 1/2) mutations, for example, ivosidenib [24], and the agents that influence the signaling pathway of fibroblast growth factor receptors (FGFRs) [25].

Table 7. Genetic profiling data for bile duct tumors from different anatomical locations

Genes	Cholangiocarcinoma, %	Klatskin tumor, %	Gallbladder cancer, %
ERBB2	4	11	16
Braf	5	3	1
KRAS	22	42	11
PI3KCA	5	7	14
FGFR1-3	11	0	3
CDKN2A/B	27	17	19
IDH1/2	20	0	0
ARID1A	18	12	13
MET	2	0	1

Dr. J.Heimbach (Rochester, USA) spoke about the experience of the Mayo Clinic with respect to patients with Klatskin tumor. In the context of

making a diagnosis, it is worth noting a routine use of cytological study, and, if possible, FISH reactions as more sensitive methods, a computed tomography (CT) and magnetic resonance imaging to determine the extent of involved vessels and ducts. Differential diagnosis is performed in all patients to distinguish from IgG4-associated cholangitis. Most often, the resection extent includes hemihepatectomy, porta hepatis resection, ductus choledochus extirpation, regional lymphadenectomy. Large centers can comply with the resection radicalism in 70-80% of cases, however, a 5- year survival rate of patients after surgery is only 43% [26]. Since 1993, the liver transplantation program for patients with Klatskin's tumor has been functioning in the Mayo Clinic. The patients with an unresectable tumor of less than 3 cm in diameter localized above the cystic duct who had no resections or transperitoneal biopsies in the previous history were selected for the program. At the first stage, all patients underwent combined chemotherapy and radiation therapy. Then the absence of distant metastases was confirmed laparoscopically. For 25 years, 211 liver transplantations have been performed using this protocol, a 10-year patient survival makes 62%. It is worth noting that the positive prognosis factors included, as it was anticipated, the explant tumor size of less than 2 cm, and the CCA development secondary to the primary sclerosing cholangitis; the patient survival rate was about 70%. Dr. J.Heimbach cited a retrospective analysis made by C.G.Ethun who came to the same opinion regarding the transplantation efficacy [27]. But no reliable prospective studies have been published to date.

Transplantation in liver invasion with metastases of neuroendocrine tumors and colorectal cancer

A resonance topic of liver transplantation acceptability in metastatic lesions was covered in two presentations with a concluding message of the prospects of the method for a carefully selected patient cohort.

Dr. J.Eason (University of Tennessee, USA) presented unpublished data from his clinic. The transplantation program enrolled the patients with neuroendocrine cancer metastases in the liver after the resection or ablation, with a Ki67 index of less than 10%, who did not progress for 6 weeks after the given treatment. While being in the waiting list, these patients had priority similar to HCC patients. Hepatectomy was performed with making the resection of the inferior vena cava or the diaphragm for a suspected involvement of these areas in the pathological process. In the postoperative period, the patients received immunosuppression without glucocorticosteroids, preferably, monosuppression with everolimus. Regular CT examinations were used to detect tumor recurrence; and the protocols based on octreotide, 5-fluorouracil, avastin, capecitabine, as well as surgical resection and stereotactic radiation therapy, were used for treatment. For 9 years, the protocol had been used in 9 patients. At the moment, a 5-year survival rate among patients is 76%, with 64% of patients having the disease-free course.

In 2015, the pilot data of SECA-1 study [28] were published, which showed a 5-year survival rate of 60% in patients without the involvement of the regional lymph nodes after a 6-week chemotherapy. At the Conference, Prof. P.D.Line (Oslo University Hospital, Norway) presented data from an unpublished SECA-2 study. It included 15 subjects who demonstrated a positive trend in response to chemotherapy; 6 patients underwent a

preliminary resection or ablation. At the time of the presentation, the median of follow-up was 36 months, a 5-year survival rate made 83%. The study by H.Grut in 2017 revealed the absence of a significant difference in the incidence of lung metastases in liver recipients compared to the control group [29]. Of the 15 patients included in the SECA-2 study, no metastases were seen in 10 cases during the follow-up. If the tumor progressed, they used aggressive surgical tactics: resections of the lung, liver, lymph nodes, and a radiation therapy. At the moment, a 4-year survival after the tumor recurrence makes 73%. Prof. P.D.Line highlights two current issues. First, the search for optimal predictors of a recurrence-free post-transplant period is underway. The attention of researchers is drawn to PET with FDG [30]. The second urgent problem is an acute shortage of donor organs; the classic way to resolve it is to use expanded criteria for graft selection. The experts from the Oslo University offered an original solution to the problem in the RAPID protocol [31], which combines liver fragment transplantation techniques and two-step hepatectomy.

Liver tumors in children

A separate session for two presentations was dealing with pediatric oncology and hepatology issues. Prof. M.Rela (Chennai, India) spoke about the positive global trends in the treatment of hepatoblastoma in children. Several years ago, the Children's Hepatic tumors International Collaboration (CHIC) was established [32] that helped in the development of optimal treatment approaches. To assess lesions in hepatoblastoma, the PRETEXT staging system [33] has been used; chemotherapy is recommended as the first stage of treatment, the response to which can be assessed after the first two cycles of treatment. The surgical intervention is recommended as a

second line, the preference is given to the resection with an optimal volume of at least 1 cm from the tumor edge. Liver transplantation is recommended for patients in whom resection is impossible due to the anatomical position of the tumor. The review presentation made by Prof. T.Hibi (Kumamoto, Japan) mainly covered the HCC issues in pediatric practice. In most cases, the tumor is diagnosed at a late stage in children of 15–19 years old, in many patients it develops in an unchanged liver. A possible example of a treatment algorithm was borrowed from R.Khanna' work of 2018 [34]. The data from retrospective studies has demonstrated that the results of liver transplantation for HCC in pediatric practice are comparable to the results of similar treatment in adults.

Conclusion

The ILTS Consensus Conference turned out to be a very rich event. In one day, leading experts in the fields of hepatology and oncology exchanged views on the most pressing issues. As key trends we should note:

- the etiological structure of hepatocellular cancer is changing. viral hepatitis is replaced by nonalcoholic steatohepatitis;

- the "transplantation as soon as possible" paradigm for the patients with hepatocellular carcinoma with a risk of an early progression has changed to the "treat and see" approach;

- a proposal is being discussed to deprive the patients with a very low risk of HCC progression of a priority in the waiting list;

- the choice of therapeutic agents for the treatment of hepatocellular cancer is expanding, and it would be great if this diversity affected recipients too;

- the molecular genetic method allows the development of fundamentally new approaches to the treatment of various liver tumors;

- the existing liver transplantation programs for patients with bile duct tumors need to be improved; meanwhile, if the tumor has developed against the background of preexisting pathology and was not differentiable at the examination stage, prognoses for patients can be quite good;

- the issues of liver transplantation for metastases of neuroendocrine tumors and colorectal cancer remain poorly studied and cause an ambiguous attitude in the scientific community;

- the tendency to unite the world experience of pediatric oncohepathology had a positive impact on the results of patient treatment.

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