HPB Surgery: Udine meets the Experts

HIGHLIGHTS

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Udine (Italy), October 01 -03, 2015

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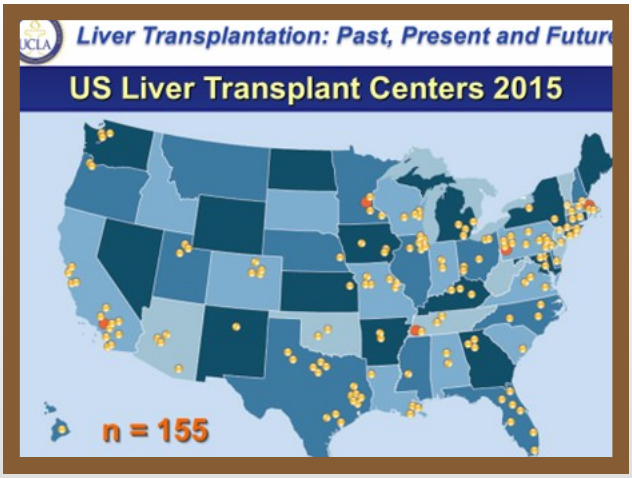
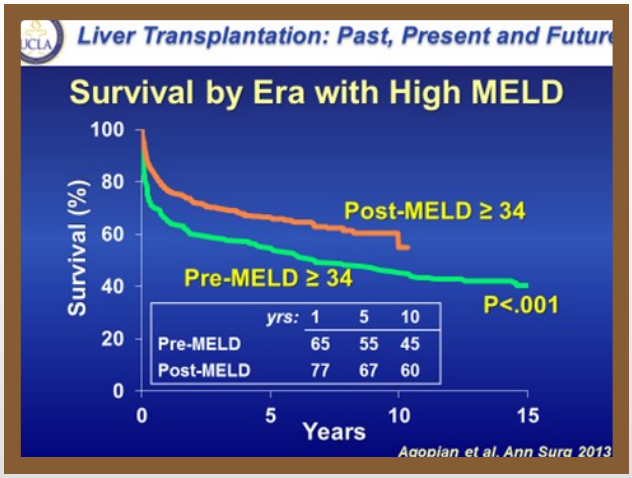
R. Busuttil
(Los Angeles, USA)

Liver transplants: past, present and future

Prof. Busuttil, Director of the Department of Surgery at the UCLA School of Medicine – Los Angeles, gave this talk by presenting a historical excursus on the topic of liver transplants, the history of which started in the fifties with Prof. Vittorio Staudacher of the University of Milano, a true pioneer in experimental liver transplantation. One of the milestones in this surgical technique is definitely that of Prof. Starzl of Denver with his first transplant carried out successfully way back in 1967. In that specific case, the patient survived for more than 6 months. The following year, in the month of May, the first liver transplant was carried out with success in Europe, and precisely in Cambridge by Sir Roy Calner. The method used was hindered for years by a series of limitations, in particular, the lack of available donors, especially for children. An initial leap in quality was made in the eighties and nineties with the development of partial liver transplantation that allowed for using "living donors". Today liver transplantation is performed in patients suffering from every kind of liver disease in the terminal stages, innumerable techniques are used, and the liver transplant centres have multiplied. Another leap in quality was made with the application of a classification model of the liver disease in the terminal stages, the so-called MELD, which has in fact made it possible to improve the prognosis of transplanted patients.





But what are the future challenges?
How can we help medical progress in this specific field of surgery?
What role can donors and patients destined to receive liver transplants play?

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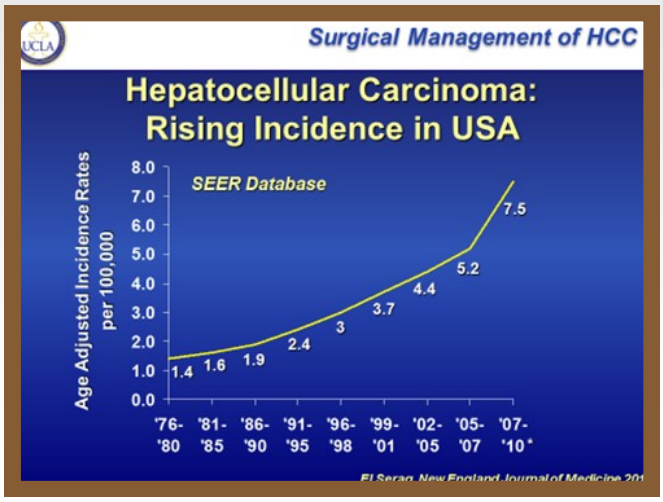
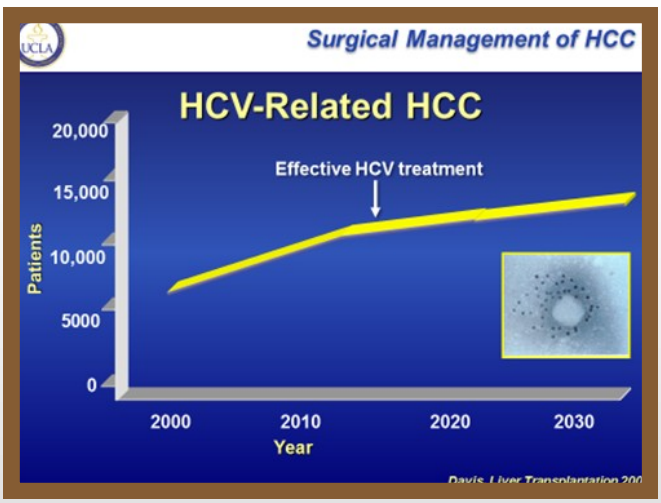
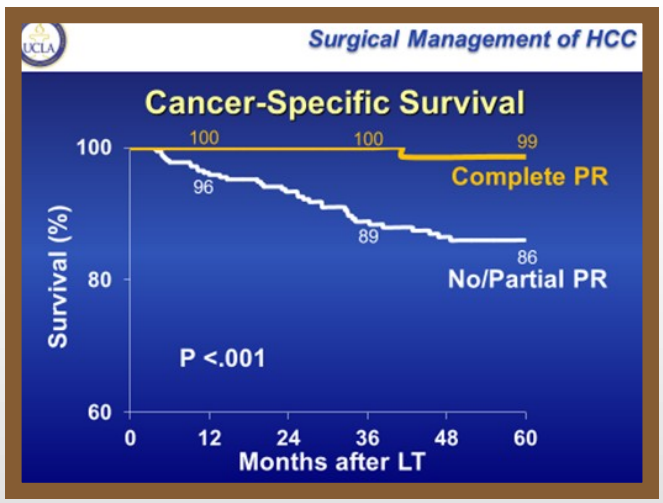
R. Busuttil
(Los Angeles, USA)

Hepatocellular cancer and liver transplants

The incidence of hepatocellular cancer is constantly rising in the world. Among the main causes, infections from the Hepatitis B and C viruses play a primary role. The key to success in reducing the incidence of hepatocellular cancer is the eradication of these viruses. While in the case of the B virus we are close to achieving our goal, only recently has a pharmacological therapy been developed that is capable of eradicating the C virus. The alternative therapeutic protocols to liver transplants are represented by the different ablation and hepatic resection procedures. Prof. Busuttil presented significant data regarding the outcome of these protocols where the relative ineffectiveness of the ablation technique compared with the resection techniques and liver transplant is clearly evident. In particular, the success percentage of liver transplantation in patients suffering from hepatocellular cancer, understood as survival for 5 years excluding death from other causes, remains stable at 99%. These alternative therapies to transplantation instead acquire a significant prognostic value if implemented during the pre-op stage in patients on the waiting list for a transplant.







What are the main causes underlying the development of hepatocellular cancer?
How useful is magnetic resonance in pre-op diagnosis?
What are the most commonly used ablation techniques?
What are the main factors that help determine the outcomes in these patients?

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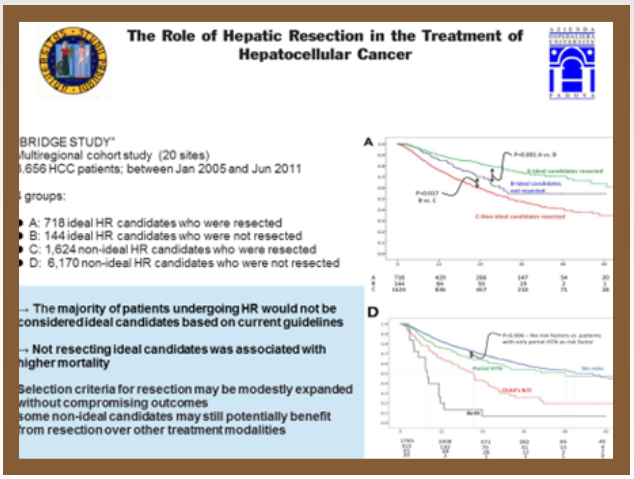
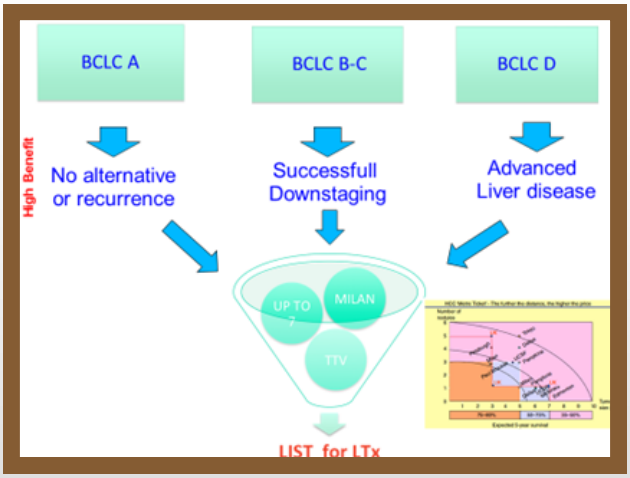
U. Cillo
(Padua, I)

Innovations in the treatment of hepatocellular cancer

As affirmed by Prof. Cillo of Padua, the treatment of hepatocellular cancer is changing radically with the introduction of new antiviral drugs. This new scenario will inevitably have an impact on the specific parameters for selecting patients who are candidates for hepatic resection, as indicated by the international guidelines. From data published at a world level, it is evident that patients classified as unsuitable for resection have a survival rate of 5 years after resection, equal to 40%. Can we deny this possibility of survival to a patient suffering from hepatocellular cancer and classified as unsuitable for a transplant? The reply of Prof. Cillo is clear: the patients must be selected on the basis of the prognostic evaluations that also take the clinical conditions of the individual into account without stopping at the indications deriving from typical statistics of *evidence based medicine*. In this way a new classification criterion is therefore established that identifies a new "prognostic objective" known as: "transplant benefit". This indicator, starting from the conditions of the basic liver disease, attributes the highest benefit to patients initially with the worst clinical picture. These are the patients who are selected for liver transplantation, namely, those who have no other valid therapeutic alternatives. This innovative classification criterion radically changes the traditional therapeutic protocols in the field of liver transplantation for hepatocellular cancer.





How many new cases of liver cancer are there in Italy?
What are the new allocation concepts for liver transplantation?
What is understood by a minimally invasive approach?

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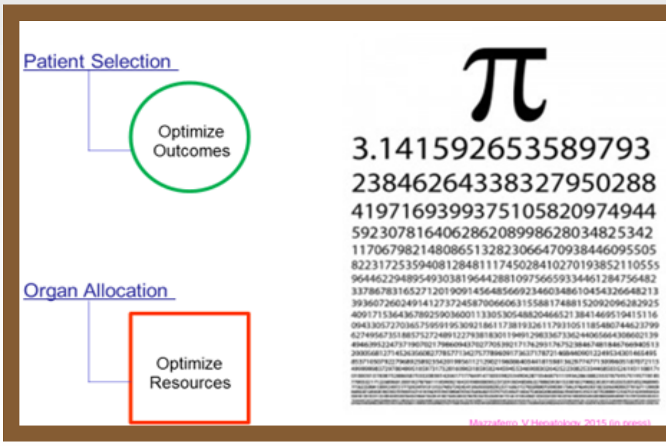
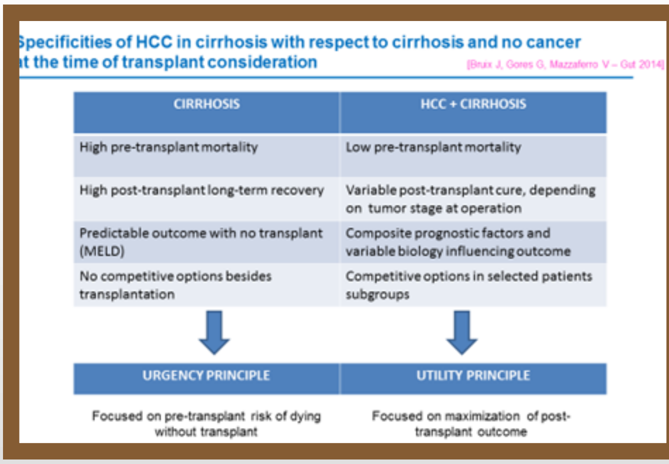
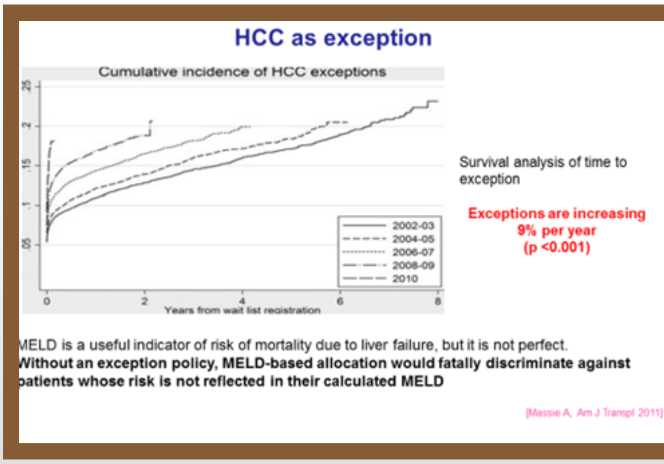
V. Mazzaferro
(Milan, I)

The future of transplants for hepatocellular cancer: beyond the BCLC

Prof. Mazzaferro of Milan addressed the topic of new criteria for identifying patients suffering from hepatocellular cancer, candidates for liver transplantation. The problem is how to combine the organ allocation criteria with the patient selection criteria. In other words, how can we optimise the organ resources that presuppose the selection of patients with the greatest life expectancy, with the need to select those patients who are in great need of a transplant? A reclassification of hepatocellular cancer is therefore necessary in the light of the greater or lesser need of a transplant. This new classification must naturally be integrated with the traditional one that is based on the stage of the disease. Prof. Mazzaferro also stressed how the future of liver transplantology for hepatocellular cancer will mark a reduction in the need for transplantation thanks to the introduction of new antiviral therapeutic solutions for treating hepatitis that will in turn give rise to a significant drop in the progression of the disease towards transformation into cancer. In this way it will be possible to have a larger selection of patients depending on the real need for transplantation compared to their life expectancy based on the scores indicated by the guidelines.







How to reconcile the patient selection with the organ allocation?
What is the relationship between alpha fetoprotein and the criteria of Milan?
MELD Indicator and Hepatocellular cancer, how much can they be integrated?

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P. Toniutto
(Udine, I)

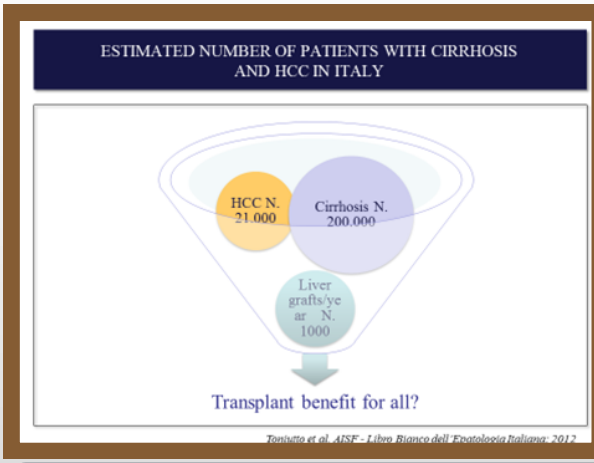
The new Italian classification of organ allocation in patients suffering from hepatocellular cancer

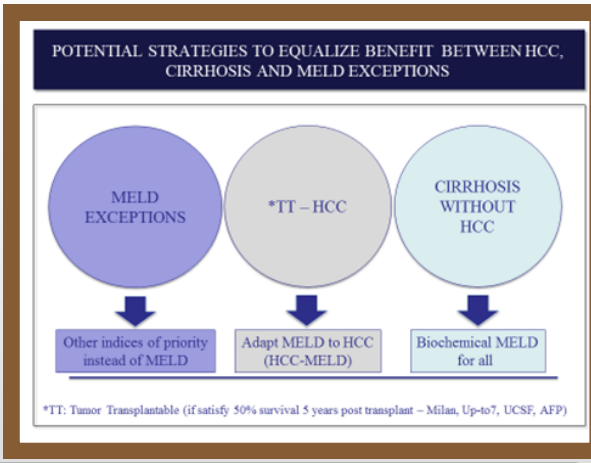
There are three models that regulate the management of transplants: the benefit model, the urgency model, and the utility model. Prof. Toniutto explained this in his interesting talk on the new Italian classification of organ allocation in patients suffering from hepatocellular cancer. The most commonly used model is the one based on urgency and regulated by the MELD indicator which presents some limitations however, including, amongst other things, the fact that it is not able to capture the severity of the liver disease just as it also fails to predict the outcome of the transplanted patient. The purpose is to find a practical solution to this patient allocation problem based on the criteria of sustainable priority. The Italian transplant centres met at a *consensus conference* at which the new criteria of the classification was identified of patients who are candidates for liver transplants, based not only on the utility model, but also by integrating the MELD with the criteria of urgency, and also that of benefit. In this way the *multistep* procedures were pinpointed that allow for guiding the complex organ allocation process with greater balance among the different selection criteria. A more appropriate priority equation was identified for balancing the different transplant requirements among patients suffering from hepatocellular cancer and those suffering from other hepatic diseases, first and foremost, cirrhosis of the liver. Finally, a new model has been proposed for assessing the benefit linked to liver transplantation in patients suffering from hepatocellular cancer based on the level of their liver function and not on the number and size of the intrahepatic carcinomatous nodules.

ALLOCATION MODELS CONSIDERED FOR LIVER TRANSPLANTATION

Model	Definition
Urgency	Focused on pre-transplant risk of dying: patients with worse outcome on the waiting list are given higher priority for Tx (based on MELD score)
Utility	Based on maximisation of post-transplant outcome, taking into account donor and recipient characteristics (D/R match)
Benefit	Calculated by subtracting to the survival achieved with Tx the survival achieved without Tx. Ranks patients according to the net survival benefit that they would derive from Tx and maximize the life time gained through Tx.

Bruix et al. Gut; 2014, mod.





What are the principal aspects of the new allocation classification?
How indicative of the new classification is the Meld?
What new outcomes can be expected?

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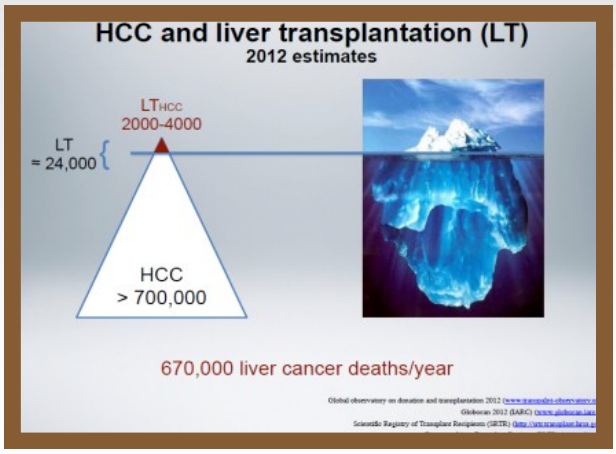
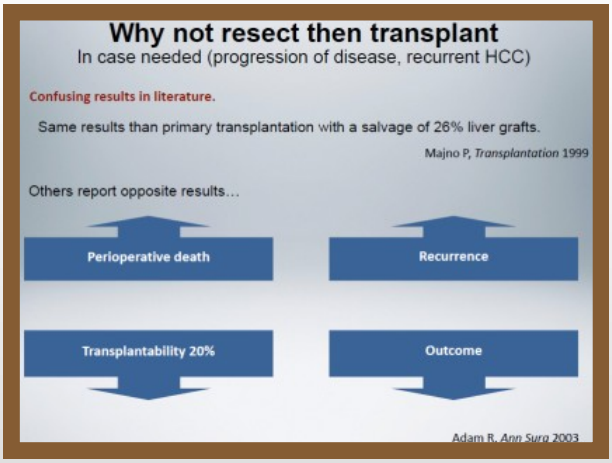
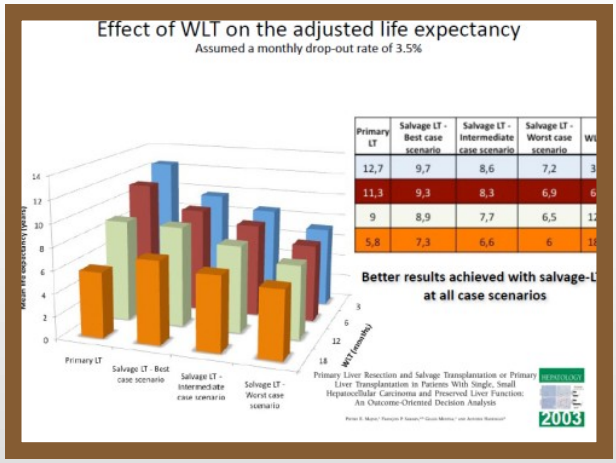
M. Sainz-Barriga
(Ghent, Belgium)

Liver transplantation: a rescue therapy

There has been an exponential rise in the number of liver transplants over recent years. The majority are performed in patients suffering from cirrhosis of the liver. Nevertheless, there has also been a significant increase in the cases of hepatocellular cancer. This condition has produced a relative prolonging of the waiting times of patients so much so that those cases of negative evolution of the disease have dropped off the list. Out of 700,000 patients suffering from hepatocellular cancer, in one year only between 2000 and 4000 patients manage to receive liver transplants. These are the figures estimated by Prof. Barriga, based on the 2012 data. In addition, post-transplant survival is significantly high, and not even comparable with the survival rate of those patients not subjected to transplants. The difference is so high that liver transplants are considered a rescue therapy. An alternative to transplants, for patients suffering from hepatocellular cancer, may be represented by hepatic resection. Prof. Barriga presented a whole series of data on the application of this therapeutic procedure both as an alternative to, and a preparation for liver transplants. Another issue addressed by Prof. Barriga was the strategy for determining the priority score of transplants that differs from country to country. In particular, it is possible to affirm that there is a series of variegated cases existing between two extremes: on one hand those patients suffering from resectable mono-nodular hepatocellular cancer with a low risk of relapses and in any case with donors available in case of a recurrence, and on the other, patients with widespread non-resectable hepatocellular cancer without any available donors in case of a relapse. The former are candidates for hepatic resection as an initial attempt, while the latter are candidates for liver transplantation.







Could resection precede transplantation?
What is the success percentage?
What are the survival estimates in transplanted patients?

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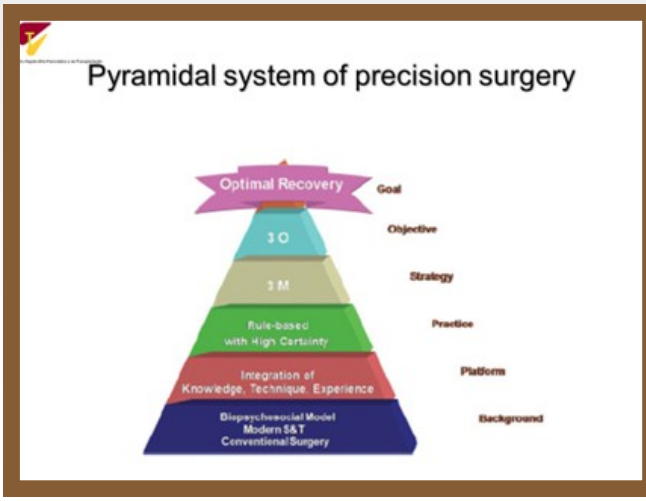
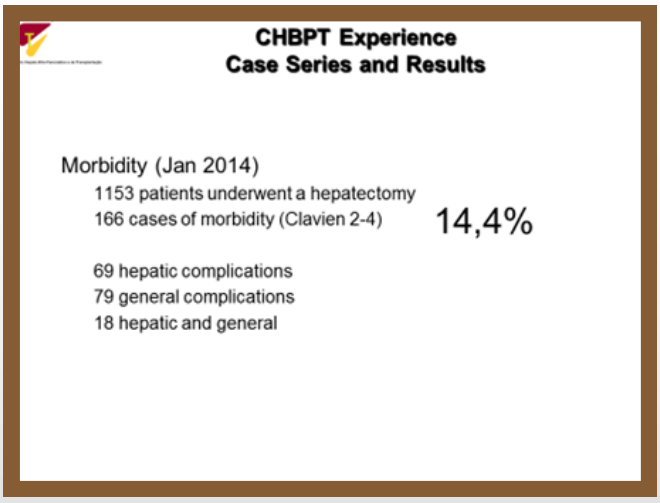
E. Barroso
(Lisbon, P)

"Precision during liver surgery": the case of liver metastases from colorectal cancer"

Prof. Barroso of Lisbon introduced the concept of "surgical precision" which does not simply mean accuracy in the surgical operation in itself, but it is also a concept that involves the entire operation of the surgical centre. Surgery has evolved after starting from a frankly intuitive and empirical dimension, and it has now arrived at the contemplation of a precision dimension based on the ability to apply high-quality surgical operations in an environment of safety and supported by a medical modal capable of combining biology with psychology and social relations. This transforms into the ability to implement extreme therapeutic strategies which are valid in case of extreme diseases. On the basis of this philosophy, even liver metastases are operated on today. At this point Prof. Barroso introduced the concept of multi-bridge therapy where chemotherapy is able to favour and anticipate hepatic resection, and where the latter acts as a bridge for liver transplantation. Prof. Barroso has obtained extremely encouraging results with this therapeutic approach: of the 9 patients operated on for colorectal liver metastases 5 are still living and have been free from relapses for nine years.





What are the typical characteristics of the "surgical precision" strategy?
What are the results of two-stage metastasectomy?
What results has Prof. Barroso obtained in his centre by applying the surgical precision strategy?

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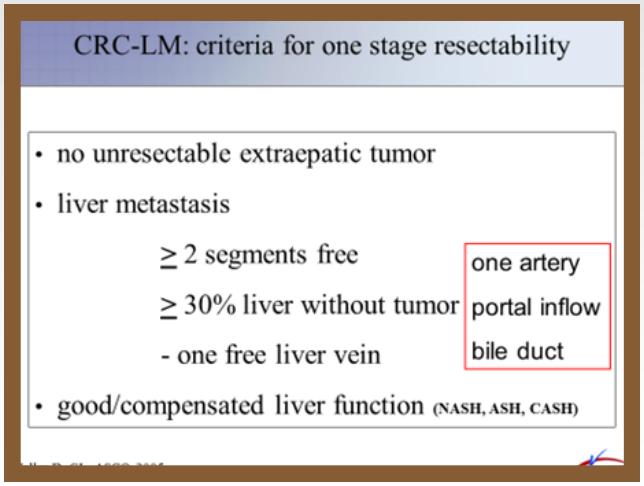
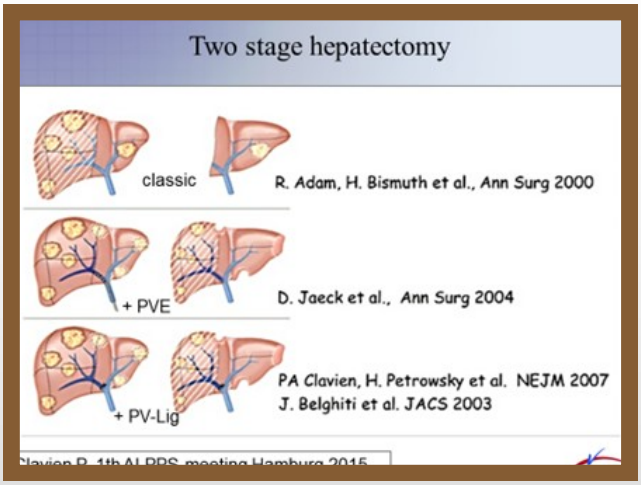
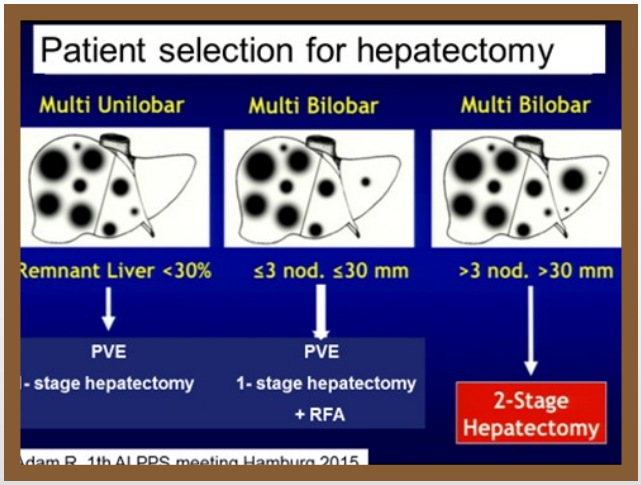
A. Konigsrainer
(Tuebingen, D)

One-stage hepatectomy compared with two-stage hepatectomy

Prof. Königsrainer presented case studies relating to one-stage and two-stage hepatectomy operations. He began his talk by explaining the difference between the two technologies. At the basis of these surgical techniques it is necessary to have an optimal radiological study in order to identify the metastatic areas. The one-stage resection can be carried out if there are no extra-hepatic cancer areas and the metastatic hepatic lesions must leave at least 2 segments free, meaning 30% or more of cancer-free liver tissue and at least one cancer-free hepatic vein, as well as showing good hepatic function. The patients who are candidates for two-stage hepatectomy are those with widespread metastases in several lobes of the liver, with more than three nodes with a diameter of > 30 mm. The first strategy to be applied in patients suffering from hepatic metastases is one-stage hepatectomy associated with chemotherapy, embolization of the portal vein and radiotherapy, while two-stage hepatectomy is reserved for patients with widespread multi-lobe metastases or with relapses following an earlier hepatectomy.







What are the main differences between the two surgical techniques?
How do we go about selecting patients suitable for the two techniques?
Two-stage hepatectomy enables better selection of patients, but what are the alternative techniques?

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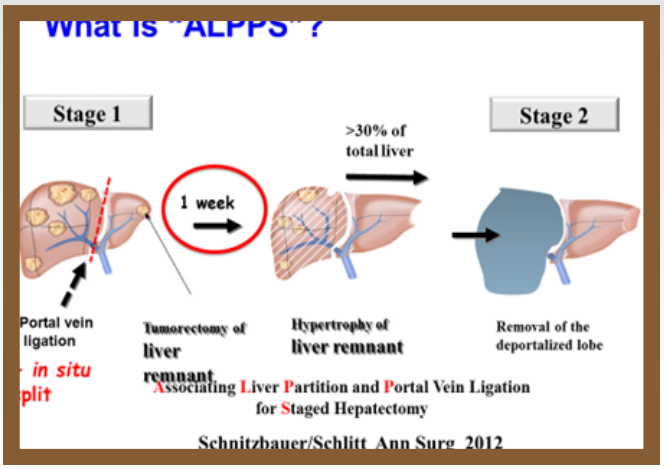
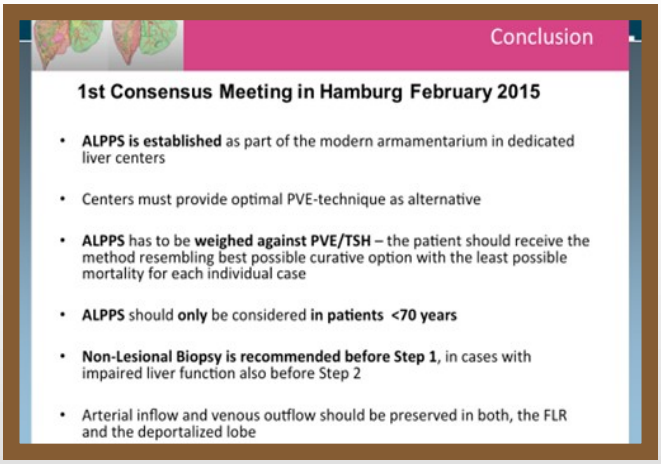
Massimo Malagò
(London, UK)

The ALPPS technique

Prof. Malagò of London analysed this currently very topical issue. ALPPS is a surgical technique based on the binding of the portal vein, the occlusion of which leads to hypotrophy of the hepatic lobe and thus becomes resectable after 4-8 weeks. But is it really true that the binding of the portal vein is the only cause of lobar hypotrophy? From data published in literature it seems that this phenomenon could also be caused by secondary trauma to the hepatotomy itself. Despite these considerations, the ALPPS technique offers unquestionable advantages compared to the classical techniques, due mainly to the possibility of removing the cancer lesions in the liver in a complete manner. The greatest problem is instead linked to an increase in the post-op mortality rate by at least 15%. But is this really true? By analysing the data of patients treated with ALPPS it can be observed how their mortality rate drops to levels no higher than 5% when they are divided according to the initial outcome of the disease. The problem therefore is that of selecting the patients before the operation. From the *Consensus* carried out in Hamburg in February 2015 it was established that ALLPS is an alternative technique that must always be performed in liver surgery centres and that before application it must always be weighed up against the other available techniques: the patients must be under the age of 70 and before the





What are the main characteristics of ALLPS? Is the patient's age really such a discriminating factor for the application of this technique? What advantages does it present compared to two-stage hepatectomy? Can this technique be applied to patients with colorectal metastases in the liver?

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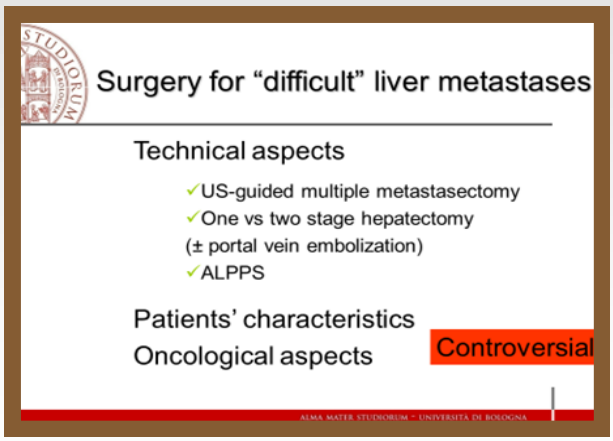
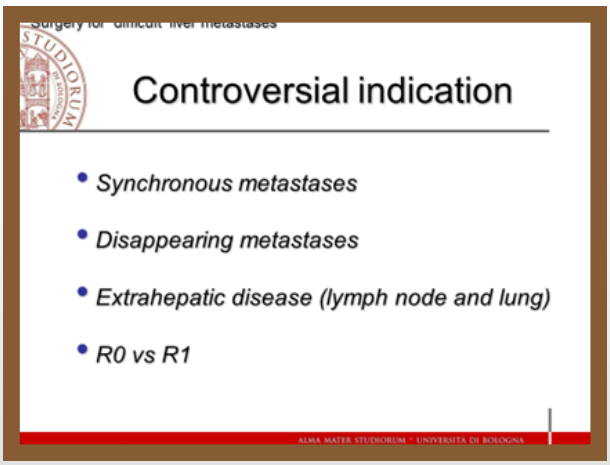
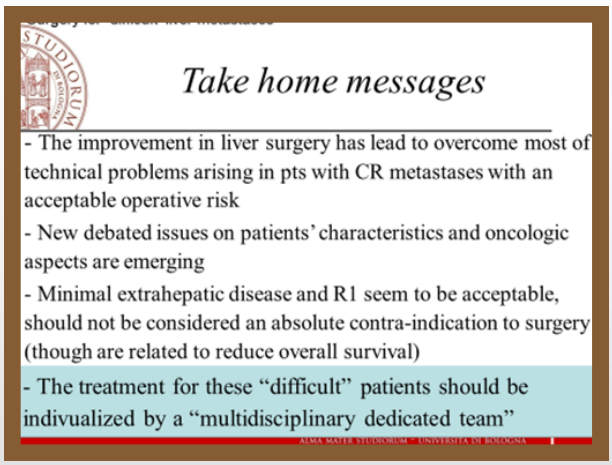
A. D. Pinna
(Bologna, I)

Difficult liver metastases

Prof. Pinna spoke about the *risk assessment* and difficult patients. The oncological controversies that make patients difficult are linked to the presence of synchronous metastases, metastases that disappear, extra-hepatic disease, and the selection of the patients based on the R0 towards R1 staging. Compared to classical multi-stage, and in actual fact, worse surgery, simultaneous surgery does not exacerbate the outcome as often as believed. What to do in patients with the disappearance of metastases after treatment with chemotherapy? By analysing the survival percentage in subjects with resected metastases compared to subjects with metastases that have disappeared after chemotherapy and been subjected to resection, this appears to be substantially super-imposable. One reference criterion is the fact of being under or over the age of 60, with the absence or presence of at least three predictive factors for the disappearance of metastases. In other words, in patients under the age of 60 and with at least three negative predictive factors it is sufficient to subject the patients to subsequent follow-ups, whereas in patients over the age of 60 with more than three predictive factors, it is preferable to intervene surgically. How to deal with the staging between R0 and R1? According to Prof. Pinna the problem is difficult to overcome because the difference between the two stages is hard to identify during the surgical operation. In his opinion, also shared by the congress assembly, it is necessary to let oneself be guided by the survival data at 5 years published in the case studies carried out for these types of patients.







What are the technical aspects that make it difficult to manage so-called patients with difficult metastases?
What are the main characteristics of these patients?
Which are the principal oncological aspects?

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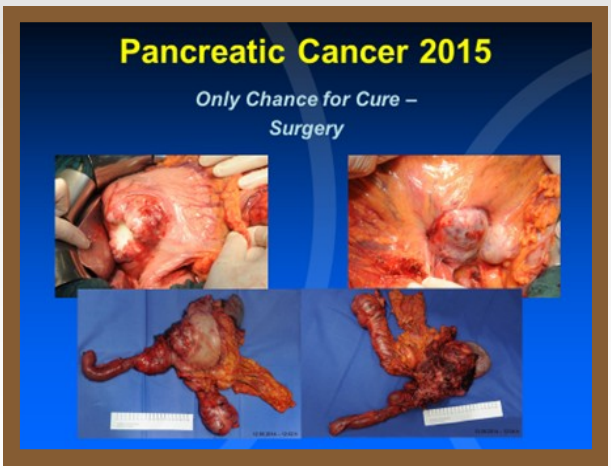
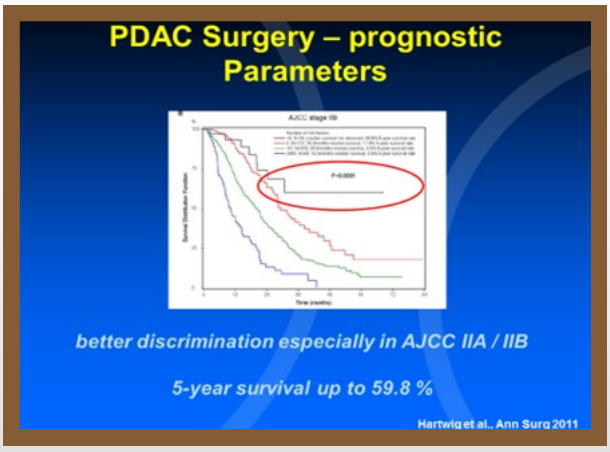
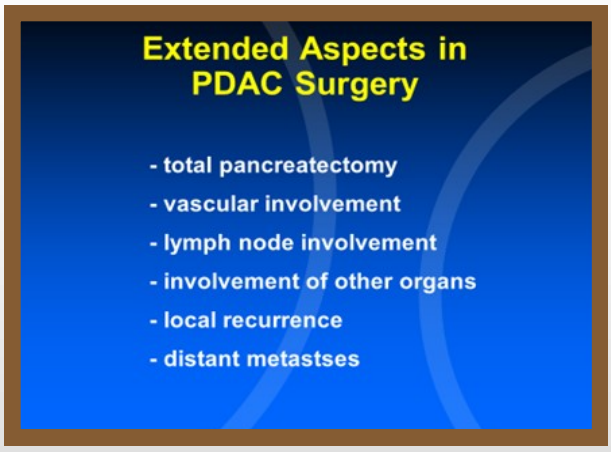
M. Buechler
(Heidelberg, D)

Extensive surgery for pancreatic cancer

"Surgery is the only possibility for treating pancreatic cancer", explained Prof. Buechler in his talk. When we speak about pancreatic cancer we often think of a single cancerous entity, but that is not the case at all: Prof. Buechler presented data taken from his case studies in which it is evident that different curves of survival exist depending on the type of cancer. However, in general at least 50% of his patients have an average survival rate of at least three years. The surgical technique has evolved over time and in the case of cancer that has infiltrated the portal vein, it can now be confirmed that also in this case the lesion can be resected and the patient will gain years of life free from cancer. Prof. Buechler also gave an accurate explanation of the surgical technique to be implemented in case of radical resection of the pancreas. However, in the event of the hepatic arterial tree being involved, can the lesion still be resected? Prof. Buechler's answer is affirmative, "Yes, it is possible to resect this lesion". In this situation part of the splenic artery will be used to regenerate the hepatic artery. The data relating to the average survival rate of patients subjected to this operation justify its implementation. Total pancreatectomy may be another option for increasing the life expectancy in these patients. The average life expectancy in these patients is influenced by the number of lymph nodes involved. Prof. Buechler presented data that demonstrate how the classical staging which differentiates the absence of lymph nodes involved (T0) and the presence of lymph nodes involved (T1), is now completely superseded.







What is the average survival rate in case of extensive pancreatectomy?
Can patients with local relapses be re-operated, what is their life expectancy?
What should we do in case of pancreatic metastases originating in other organs?
What is the future of pancreatic surgery?

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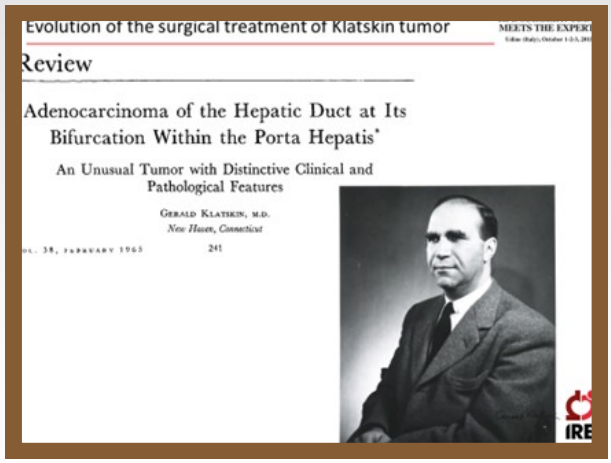
HPB Surgery: Udine meets the Experts
Udine (Italy), October 01-03, 2015

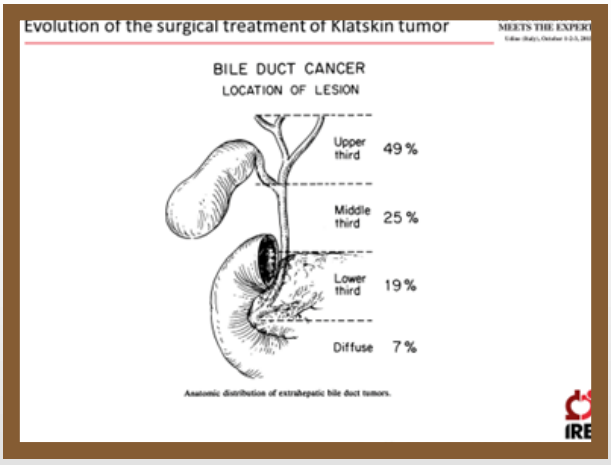
HIGHLIGHTS

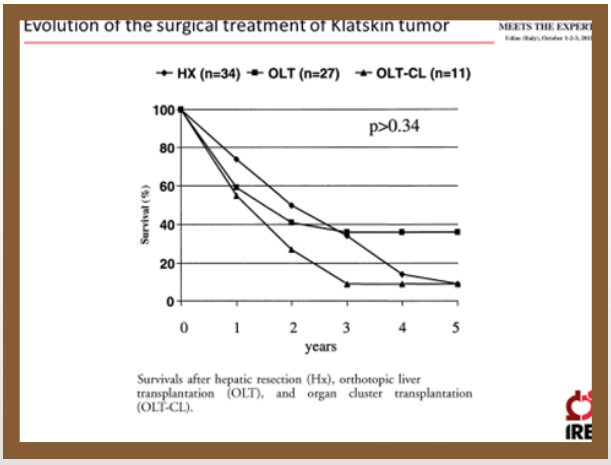
G. Grazi
(Rome, I)

The evolution of surgical treatment of cholangiocarcinoma

Prof. Grazi of Rome addressed this topic starting from its beginnings in the nineteen-fifties and sixties in the United States where Dr. Gerald Klatskin was the first surgeon to publish a scientific article with a description of the adenocarcinoma, very rare for those times. This researcher spoke about a cholangiocarcinoma that had developed at the bifurcation of the main bile ducts. From that time on this cancer was named after him: Klatskin's tumour. In the nineteen-eighties treatment of the cholangiocarcinoma also began in Europe, in particular in Hannover, where Prof. Rudolf Pichelmayr published data on 125 resections and 25 transplants with excellent results in terms of survival. Meanwhile, in the United States, Prof. Staltz and Prof. Iwatsuki presented equally interesting data in terms of survival, especially after liver transplantation. The real leap in quality in the treatment of this kind of cancer was made when Japanese surgeons also entered into the picture. Thanks to the radical approach they applied, the survival curve increased significantly. Today the standard treatment of cholangiocarcinoma is extensive right or left hepatectomy caudate lobotomy and excision of all the nerve and lymphatic tissues inside the hepatoduodenal ligament. The main problem with this surgical technique is linked to its radicality that does not always allow for complete application with consequent peri-post-op mortality that is anything but perfect.







What are the main forms of cholangiocarcinoma?
What is the evolution of the surgical treatment of this kind of cancer?
What are the pros and cons of *stenting* of the bile ducts?
Are these patients receiving the best possible surgical treatment?

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HPB Surgery: Udine meets the Experts
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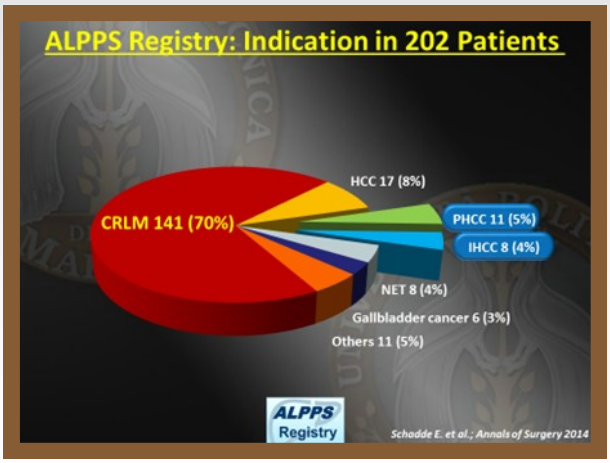
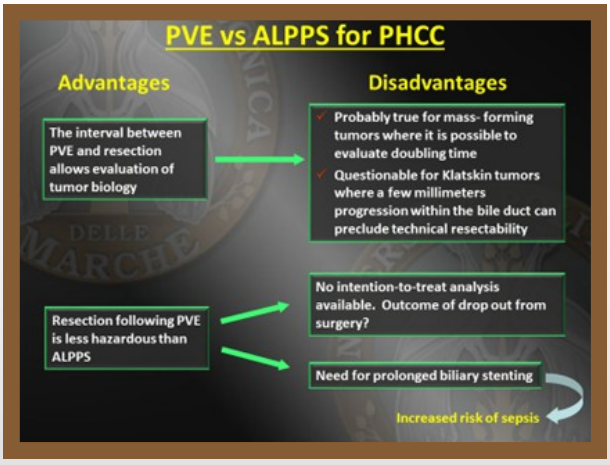
HIGHLIGHTS

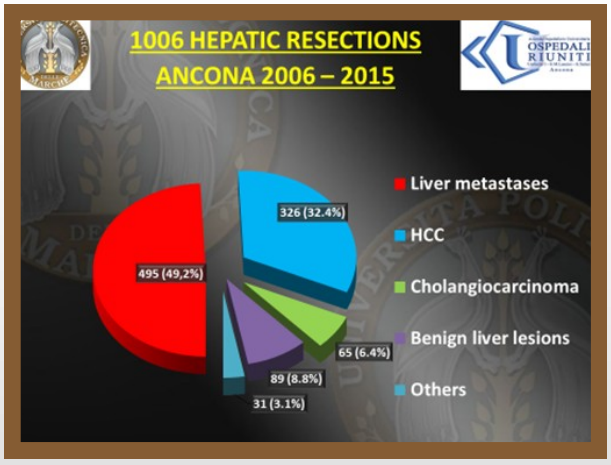
M. Vivarelli
(Ancona, I)

ALPPS for cancer of the bile ducts?

Prof. Vivarelli of Ancona addressed this topic by presenting data that is insufficient for drawing definite conclusions. To date, no specific articles have been published on ALPPS applied with perihilar cholangiocarcinomas. The data garnered from the registers show an unacceptable mortality rate, nevertheless, it is necessary to bear in mind that these tumours are also exacerbated by a high post-op mortality rate. What are the pros and cons of the application of ALPPS in the treatment of these tumours? Prof. Vivarelli ventured into this problem without however being able to give a definite answer to the opportunity or otherwise of applying ALPPS to this kind of cancer. He therefore presented his case studies, dwelling in particular on the case of a patient suffering from Grade IV cholangiocarcinoma and with a "future liver remnant" equal to 22%. The application of ALPPS gave extremely positive results: the patient currently enjoys good health and has been free from hepatic cancer lesions for 33 months. In the light of the data presented, according to Prof. Vivarelli, it is possible to apply ALPPS with caution in the presence of cholangiocarcinoma, although not in all patients. In particular, patients over the age of 70 with hepatic fibrosis should be excluded from the biopsy, and also those with concurrent diseases with a high clinical impact.







What are the pros and cons of ALPPS in patients suffering from cholangiocarcinoma?
Why do these patients have a high risk of developing post-op inflammatory complications?
Can the techniques for facilitating ALPPS be used in this type of patient?

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HIGHLIGHTS

These are some of the topics addressed during the congress talks. For more in-depth information please visit the website of the Fondazione Internazionale Menarini which contains the full versions of the congress talks.

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