Professor Javier C. Lendoire: colorectal liver metastases

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Professor Javier C. Lendoire (Figure 1) is currently Professor of Surgery at the University of Buenos Aires, Vice Chairman of the Liver Transplant Division at the Hospital Dr Cosme Argerich, Buenos Aires, and Chairman of the Liver Transplant Unit at Sanatorio Trinidad Mitre, Buenos Aires. He has been an active member of different surgical societies. He was a founding member and Past-President of the Argentine Society of Transplantation. He became a Council Member of the Argentine Chapter of the IHPBA (CA-IHPBA) since 2003 and he is Secretary of the AHPBA and the Argentine Society of Surgery. He serves on the Scientific Committee for the IHPBA and he is an active member of the Argentine Surgical Academy. His practice is focused in liver surgery, complex biliary surgery and transplantation.

Figure 1 Professor Javier C. Lendoire.

HBSN: Could you please give a brief introduction about the current status of the management of colorectal liver metastases in terms of research?

Prof. Lendoire: In this meeting I had to discuss the issue of how to extend the limits of resection for colorectal liver metastasis. We still have limits at the present time but were clearly expanded more during the last years. Limits are basically related to the oncological and technical criteria of resectability. Presence of extrahepatic disease and progression of metastatic disease in patients with optimal chemotherapy are relevant oncological limits. In terms of the technical criteria the expectation that a margin negative can be achieved and the ability to preserve and adequate liver remnant in terms of volume and function still remains as technical limits for the application of resection in this kind of patients. Presence of extrahepatic disease changed from an absolute contraindication to a negative prognostic factor for liver resection. Most frequent localizations are peritoneal, lung and lymph node metastases. Curative resection of the intra and extrahepatic metastatic sites offers a 25% median 5 year survival. Selection of patients is still critical and there are clear differences in the comparison with the resection of patients without extrahepatic disease like the lower preoperative diagnosis and the higher rate of R1 and R2 resections. Prognosis is still a matter of discussion and it seems the two more critical parameters are still location and the number of extrahepatic metastases. We should consider that the most important factor that is changing our views in this disease is chemotherapy and we should analyze the evidence we have with this concept.

The second topic discussed, part of the technical limits, was the functional liver remnant. The first procedure used to increase the volume of the future liver remnant was Portal Vein Embolization. This procedure brought more patients into the field of liver resection. It demonstrated progressively to be a safe method to induce hypertrophy of the remnant liver, which allowed us to do extended resections in an increased proportion of patients with advanced metastatic disease who would have dismal prognosis without surgery. Resection of liver metastases after Portal Vein Embolization demonstrated resectability rates from 60% to 82% and 5-year survivals from 25% to 46%. Then, the problem of liver remnant extended to another kind of patients, which have bilateral metastatic disease and were not candidates for bilateral

single resection or portal vein embolization plus resection. In this group of patients, the procedure that was first applied was the "two-stage hepatectomy". The evolution of two-stage hepatectomy started with the first type of these procedures where first a Major and then a Minor resection were performed. In the second type of 2-stage hepatectomy portal vein occlusion was added to the minor resection in the first stages. The period of time between the two stages ranged between 2 and 3 months and there was a 24-29% failure rate reported to complete the second stage. Finally became ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy) with the same sequence described for the second type but including a parenchymal transection and a rapid functional liver remnant hypertrophy.

The third limit described was the margin. There was a progressive reduction in the margin required for resection of colorectal metastases till the last studies that sustained a benefit with any negative margin. At the present time margin width does not impact on outcome and the 1 cm rule is no longer a contraindication for a liver resection. We have to points to analyze. My first point refers that it is clear that the margin have a relation with the anatomical localization of the tumors and the type of procedures you are doing in the liver. Resection line can be closed to the vessels and the tumor itself when there is no other option. Some parenchymal transection devices give you an extra margin and it is clear that higher resectability rates are associated with a higher incidence of positive microscopic margins (R1). Recent data of R1 resections showed survival benefits but with a higher intrahepatic recurrence rate on this group of patients. Chemotherapy is playing a key role in the treatment of this group of patients.

HBSN: You said that you have two points. Then what's the second point?

Prof. Lendoire: My first point analyzed was from the perspective of the liver disease itself. My second point is in reference to chemotherapy. The incidence of R1 resections presents a wide spectrum ranging from 5% to 46% in six different studies. Only 2 of these studies showed comparable survival between margin negative and margin positive resections. So at the end, there was a benefit for these patients, but less than for those patients with negative margins. There is a need, at the present time, to anticipate patients with positive margins and give them chemotherapy in advance. Better results had been demonstrated in patients with a morphologic or a pathologic response to chemotherapy in this setting.

HBSN: You talk about the treatment of patients just now and also the selection of patients in your presentation. So what do you think are the key factors for finding defining the selection of patients for chemotherapy?

Prof. Lendoire: Actually this is a very important topic with a lot of debate. First I should say we need to discuss about chemotherapy in the easily resectable patient. Should we go first to chemotherapy or to resection? There are lots of discussions on this aspect but there is still a lack of evidence in favor of neoadjuvant chemotherapy and resection remains the best curative approach in this patients. Different are the marginal resectable patients. This topic has been discussed over the years and we can say that we had reach a consensus that chemotherapy should be our first choice in this group but limited for a short period of time previous to resection. Here is where the selection starts according to the chemotherapeutic response. Chemotherapy has a real value as a rescue therapy in other group of patients that presents with irresectable disease. Downsizing allowed us to perform resection with long term survival in these patients. The success of this approach should be mirrored by an increased rate of resectable metastases. A critical aspect is still the histological changes of the liver parenchyma induced by chemotherapy including steatosis, steatohepatitis or sinusoidal injury. In the setting of extended surgical resection, preoperative chemotherapy may contribute to the development of a small-for-size syndrome and fatal liver failure.

HBSN: You mentioned more than chemotherapy advances in your presentation. Could you please give some details about that?

Prof. Lendoire: Modern management of hepatic colorectal metastases necessitates a multidisciplinary approach to effectively treat these patients and increase the number who will benefit from resection. The expansion to new technical strategies of resection had given complementary roles to chemotherapy. Also the management of patients with extrahepatic disease had changed, but more efficient regimens are needed to improve results of surgery in this group of patients. Considering more complex patients are candidates for therapeutic interventions the multidisciplinary discussion is the key to select the best

therapy in each new patient.

HBSN: What do you think is the cutting-edge frontier of liver metastases research?

Prof. Lendoire: I don't think there is any frontier. I think there are lots of things to be done and to be discovered. But we should be careful when we look at the frontier. There are a lot of new developments, new techniques, and new options. But we should take care of the new developments and the decision-making should be based on the best evidence we have. We should be careful not to take out the patients from the traditional and well-known therapies since the evidence is strong in favor of a change.

HBSN: What can be expected in the future development of liver metastases?

Prof. Lendoire: The tendency should be to improve results of chemotherapy broadly. It seems that resection reached the limits but chemotherapy still has the potential for future development of new strategies. As an example, it is clear that in non-colorectal metastases new chemotherapeutic regimens are required to achieve better results according to the anatomical site of the primary tumor. Especially in this group of patients, surgery must be a complement of an appropriate chemotherapeutic treatment. Also new molecular markers with prognostic value are required in this entity.

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HBSN: Do you think the latest development of liver metastases research can be applied to clinical research and help our patients now or do you think it is still difficult to do so?

Prof. Lendoire: I think it's complicated for latest developments of liver metastasis to be applied immediately to clinical research. It depends on the research itself, the evidence showed and the selection of patients that require the treatment proposed. The application of a new surgical or medical therapy should be performed after randomized control trials that demonstrate its benefits. This is not uniformly applied, so we need to have more caution in the application of therapies with less evidence. As I said before, in these cases we need to do it progressively with a lot of revisions, resizing and comparing each new method with the standard ones. An example we have with the new techniques that have being implemented for the insufficient future liver remnant and are still under evaluation as I showed in my presentation.

HBSN: Thank you very much!

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