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Review Article

The Challenge of Liver Metastases: Evolving Knowledge and Treatment

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Abstract

The liver is a common site of metastasis for many different tumours due to its anatomical, immunological and metabolic characteristics. For years, metastatic disease, even if oligometastatic, for many tumours was a definite limitation to the surgical option and curative intent. In recent years, the range of therapeutic options for both surgical and ablative and oncological treatment has expanded enormously. New surgical strategies to make what is initially not surgically treatable have emerged in the treatment of metastases, and new innovative medical therapies that rely not only on the local response but also on the systemic response of the patient are outlining exciting future scenarios leading to a complete evolution and revolution of the concept of metastases.

Introduction

Liver metastasis represent a big challenge in the battle against cancer because they have a high mortality rate. They are very common and they have a higher incidence than the liver primary tumors. Liver metastasis from colorectal cancer are very frequent and often represent the only site of metastasis. Around 30-70% of patients die with liver metastasis and metastasis are responsible for more than 90% cancer mortality. Much progress has been made in the management of the patients with liver metastasis. Surgical techniques and strategies have made many more patients resectable and in some cases even transplantable than in the past. Many studies have been done to make secondarisms resectable, which not long ago were considered untreatable. Furthermore, the locoregional strategies offer an excellent treatment in a less invasive way or for lesions that cannot otherwise be treated.

Metastasis Mechanisms, Seed And Soil Theory

From Paget's theories on seed and soiling to the study of hemodynamic factors that can explain blood diffusion by proximity or by type of vascular anatomy, (Edwing), the definition of organotropism involves many other recently discovered mechanisms [1]. A complex interaction of events both locally (Warburg effect, reverse Warburg effect, metabolic symbiosis and cancer immunoediting) sistemically as well as specific aspects of the target organ are jointly involved [2-6].

Tumor and tumor microenvironment start defining organotropism and pre-metastatic niche

Communication between neoplasm and perineoplastic tissue is probably the first step in the cascade of multiple events that lead to the development of metastases and occurs in the very early stages of the development of the primary disease. The definition

of tumor microenvironment through the cellular and non-cellular components involved allows the understanding of multiple key points involved. The role of the local immune response, probably the first barrier encountered, is well known. The first response mediated by CD8 + T cells is easily neutralized both by overexposed metabolic mechanisms and by mechanisms that the neoplasm is able to inject to increase its metastatic capacity (macrophages deriving from hematopoietic stem cells: TAMs). TAMs are in turn involved in local progression and in the phenomenon of disease spread by activating the epithelial to mesenchimal transition. At the local level, the set of these phenomena and cell types defines the Tumor Microenvironment of Metastasis (TMEM). Mesenchimal stem cells are also involved in the process and are part of the tumor microenvironment through their ability to modulate the epithelial-mesenchimal transition and favoring neoangiogenesis; they are also capable of producing exosomes [7]. The extracellular vesicles of which the exosomes are part but also the microvesicles and apoptotic bodies have recently been identified as responsible for very important roles at the level of the tumor microenvironment, contributing through their load to the development of metastases and to the selection of organotropism. The signal mediated by microvesicles allows an exchange of intracellular information with the possibility of modulating the migratory and metastatic behavior of more quiescent cells but also of inducing drug resistance. They are also able to reduce the immune response by increasing the development of immunosuppressive cell populations (PD-1 positive nonclassical monocyte) reprogram the cellular metabolism of neoplastic cells which is a fundamental step in the extravasation and dissemination of tumor cells.

MiRNAs belong to the 'family' of non-coding RNAs (ncRNAs) which are fragments of RNA that have different roles. MiRNAs are short single strain of RNA produced by human genome. Since 2007 several studies have been performed showing important role at many steps. They are able to act through regulation of oncogenes, tumour suppression genes, metastasis genes, cancer stem cells properties, epithelial-mesenchymal transition, microenvironment and exosome secretion [8]. To the same group of nc RNA belong the long non-coding RNA (lncRNA), about ten times larger than miRNAs. Recently, attention has been paid in particular to the cross talk between these two structures. Epithelial-mesenchymal plasticity was found to be an important node in the progression of neoplastic disease. This phenomenon of bidirectional biochemical changes, in the epithelium-mesenchymal or mesenchymal-epithelial transition has been found to be involved in the different steps, from local invasion to extravasation, up to the colonization of metastatic sites at a distance. MiRNAs have dual roles regarding the control of epithelial-mesenchymal plasticity. Both sequences with suppression and activation activities of the epithelial-mesenchymal transition have been identified. While microRNAs act only at the posttranscriptional level, lncRNAs act at various levels both transcriptional and post-transcriptional. In addition, some lncRNAs can also produce miRNAs but above all miRNAs and lncRNAs interact with each other by modulating EMT and MET plasticity and consequently influencing tumor progression [9].

An important stromal component is fibroblasts. They derive from different cell types and through activation by cancer cells constitute in TME the population of Cancer-Associated Fibrobalsts (CAFs). They are able to modify the structure of the extracellular matrix of TME by releasing fibronectin, collagen and modulating VEGF levels, to make TME more suitable. They also have a modulation function in an immunosuppressive sense. Lymphatic spread for many tumours (including colorectal cancer) occurs even before hematogenous spread. Recent studies have deepened the topic overcoming the conception of a mere mechanical process of transport of cancer cells from the primary tumor to other districts but rather of an active role of interaction between Lymphatic Endothelial Cells (LECs) and tumor cells. In fact, neoplatic cells are able to activate LECs by producing IL-6, thus activating the lymphatic diffusion. The first invasion phenomena derive primary from the mechanical invasion due to the growth of the tumor and secondly, however, from the lymphangiogenesis induced by the neoplastic cells. Following the achievement of the lymph nodes and the overcoming of the immunological barrier at this level, it is interesting to note that the diffusion at this point occurs both lymphatically and hematogenously, through the efferent capillaries of the affected lymph nodes [10,11]. However, in the tumor microenvironment factors are produced that stimulate lymphangiogenesis (e.g. VEGF-C) and many other molecules capable of modulating the phenomenon of lymphangiogenesis (EGF, EPO,..) [12-15].

In addition, lymphangiogenic factors are also produced following the local peritumoral inflammatory stimulus. The extracellular matrix is also actively involved. These phenomena in turn are responsible for a remote communication through secretion of VEGF-C or other mediators that communicate with LECs of distant organs by initiating the process of prometastatic niche formation even before the cancer cells have actually reached the target organs [11]. Procoagulant activity is another factor involved in the progression of hematogenous metastases. More precisely, the activation of the coagulation cascade is involved both in the growth of the primary tumor and in the development of its microenvironment and in the progression and dissemination of disease. Platelets, coagulation proteases, thrombin-induced platelet activation and fibrin formation are involved in these steps [16,17].

At local level, in the tumor microenvironment, the vascular permeability can be enhanced by neoplastic cells through generation of VEGF with the local formation of thrombin and fibrin deriving

from the contact between plasma circulating proteins that come into contact with plasmatic membranes of neoplastic cells rich in procoagulated molecules such as TF (tissue factor), the central trigger of the coagulation cascade and PS (phosphatidylserine), while the intravscular system is reached by micirovescicles secreted bu tumour cells exposing PS that can activate coagulation cascade with formation of thrombus in the intravascular system. The correlation with thrombotic syndromes and thrombophlebitis has been known since 1860 with the description of Trousseau and the subsequent identification of paraneoplasty thrombotic syndrome that bears his name [17]. The extracellular matrix of the tumor microenvironment is equally involved. It is composed of proteins and macromolecules (immune cells, fibroblasts, capillaries, and fibrillar proteins, such as collagen I, elastin, and fibronectin, as well as hyaluronan and other sulfated glycosaminogly) that perform a structural and biochemical function and that in the normal condition can initially act as a barrier for neoplastic cells. However, with the development of the primitive tumor the extracellular component changes with changes in the constitution and density. The establishment of a fibrotic response is one of the main characteristics that is created with the excessive production of collagen mediated by the activation of CAFs in response to the stimulus of TGFbeta. A local condition of stiffness and mechanical compression is thus created, called solid stress. On the other hand, a second component of forces develops in the host tissue in the direction of the tumor to resist tumor expansion and is known as externally applied stress. The presence of these mechanical factors creates more central less vital areas but more peripheral areas that instead demonstrate a more proliferative and migratory behavior, suggesting that progression and spread also depend on mechanical factors of local and periwound compression that is established in the tumor microenvironment [18].

'Secondary Soil Aspects', Premetastatic Niche and Liver Organotropism

The organotropic development of metastases is regulated by multiple factors. It is now well known that the metastatic site is selectively and actively prepared with a sort of 'preconditioning' that occurs through the information exchanged between the primary tumor and the primary soil with the secondary soil before the circulating tumor cells actually reach it. The set of phenomena of this preconditioning is called Premetastatic Niches (PMNs) and were described for the first time by Kaplan, R. N. et al. [19]. Pre-metastatic niche is defined as a tumor cell-free microenvironment in a putative organ of metastasis [20-22]. The importance of the concept of premetastatic niche has found in recent years great scientific attention and interest. Its characteristics have been divided into 6 categories: inflammation, immunosuppression, angiogenesis and vascular permeability, lymphangiogenesis, organotropism and reprogramming [23-27]. The three major factors for the definition of premeteastatic niche can be summarized as follows: 1) primary tumor-derived components which include Tumor-Derived Secreted Factors (TDSFs), extracellular vesicles and other tumor-derived molecules;2) bone marrow-derived cells which are recruited and mobilized by tumor cells; 3) stromal microenvironment.

1) Tumor derived secreted factors are able to recruit and mobilize myeloid cells from the bone marrow to the pre-metastatic niche but can also modulate the primary tumor micronvironment promoting paracrine migration and colonization by myeloid cells from the microenvironment to distant organs by defining premetastatic niche. Tumor derived extracellular vescicles are able to modify and form the micronvironment of the distant organ to form a tumor promoting soil and direct BMDCs to form a premetastatic niche; tumor derived cytochines, chemokines and inflammatory factors are also involved in the formation of premetastatic niche recluting TAMs and Tregs and last helping circulating tumor cells to reach and invade the niche.
2) the recruitment and mobilization of BMDCs and several immune cells reshape the microenvironment by secretion of inflammatory cytokines, growth factors and proangiogenic molecules, making it premetastatic soil.
3) the role of the stromal component of the target organ is equally important; it consists of a large amount of heterogeneous cellular and molecular structures, as well as an extracellular and vascular matrix that has not only the function of support but also of maintenance of homeostasis; during the evolution of the neoplastic disease it is also remodulated and 'educated' to support the future development of metastatic colonies [24,25].

Some recent work on some epithelial neoplasms (breast and pancreas) whose metastases have organotropism for the liver in particular, have highlighted some interesting factors: epithelial characteristics, in particular can determine hepatic organotropism rather than pulmonary one; hepatic organotropism for pancreatic ductal adenocarcinoma depends on P120 catenin epithelial plasticity (P120CTN).

Integrins and chemokines are able to define hepatic organotropism for colorectal and breast cancers. Lymphocyte function-associated antigen-1 (LFA-1) is related to the development of liver metastases from colorectal cancer as it is an integrin with adhesion functions that is used by immune cells to invade the hepatic parenchyma during inflammatory conditions. In vitro studies have shown that the decreased expression of a subunit of this integrin and that it is necessary for its activation and activity correlates with a lower activation of the hepatic endothelium and with a better immune response in the liver; this, in turn, results

in a reduction in metastatic development and size [28]. In breast cancer it has been shown that the link between a chemokine and its receptor (CXCL12 and CXCR4) is related to the ability to induce liver metastases and promote the extravasation of cancer cells. The presence of integrin complexes (α2β1 and α5β1) on the cellular menbrane interacts with the hepatic stromal structure; downregulation of the presentation of these complexes would be related to a decrease in the development of hepatic metastases due to a lower interaction between cancer cells and the extrcellular matrix [28].

Still involved in the construction of the pre-metastatic niche we find other actors: exosomal integrins, lipid droplets, cancer stem cells, neuropepetides. Exosomal integrins are secreted from tumor cells and participate in the definition of the pre-metastatic environment.

Cancer stem cells that have a strong ability to migrate are able to establish a cross talk between primary tumor and target organ, helping in turn to modulate the formation of the pre-metastatic niche [20]. Lipid droplets have the peculiar characteristic of acting as specialized hubs of inflammatory mediators in leukocytes (e.g., macrophages, neutrophils, and eosinophils), inducing immune suppression or immune surveillance, increasing angiogenesis and vascular permeability in the pre-metastatic niche [18,27,28]. LDs have properties that affect both cancer cell sand stromal progression in the PMN [29-32]. The stage at which the process of preconditioning the future metastatic site begins is not certain. Some studies have highlighted the presence of mediators involved already in the very early stages or even in conditions of preneoplastic pancreatic lesions, suggesting a very early timing in the onset of the phenomenon [33] (Figure 1).

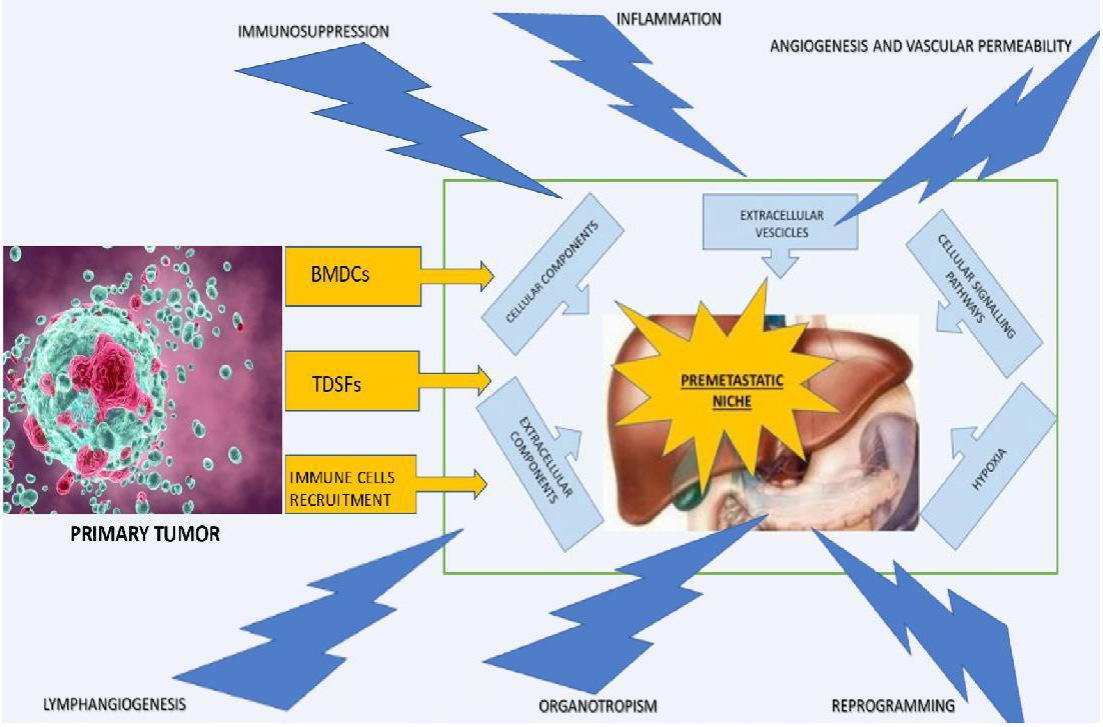

Figure 1: Premetastatic niche characteristcs and formation via tumor derived actions and through phenomena activated in the micronvironment of the target organ. BMDCs: bone marrow derived cells; TDSFs: tumor derived secreted factors.

Prometastatic Reaction and Interorgan Crosstalk

The liver is a fundamental metabolic center as many processes of production and storage of energy sources originate at this level. Its vascularisation results in a hypoxic environment, as portal flow is much higher than arterial flow [34].

The hypoxic environment is a prometastatic feature, as neoplastic colonies are able to mimic this behaviour by entering into metabolic competition with normal liver cells; this fact, together with the hepatic vascular anatomy the sinusoidal permeability and the ability to modify the peculiar transcription program of circulating cells through the action of enhancers or superenhancers, making it similar to that of the liver [35] may explain the frequency of metastasis to this organ. In colo-rectal cancers, metastatic cells are able to upregulate the expression of a brain-type creatine kinase and secrete it into the liver metastatic microenvironment, phosphorylating creatine to produce phosphocreatine [36]. Phosphocreatine is then used in place of the intracellular ATP of metastatic cells allowing their survival. In breast cancer, metastatic cells have learned to modulate glycolysis and tricarboxylic acid cycle activity levels, with specific target organ mechanisms. However, compared with that of bone and lung metastasis in the liver there is a greater glycolytic activity, the oxidative phosphorylation and glutamine metabolism are weaker, which promotes adaptation of cancer cells in the hypoxic environment [37]. Furthermore, the activation of intrahepatic cells can modify the metabolic behavior of metastatic cells. In particular, stellate cells, normally quiescent, when activated in a context that from poorly inflammatory becomes inflammatory can affect their metabolic state, proliferation ability and stem cell characteristics. Also ketone body metabolism, enterohepatic circulation of bile acid, and ammonia metabolism, may change the metabolic behaviour of cancer cells [38].

Together with the systemic effect (e.g. paraneoplastic sdr) the organ-specific response activated by the neoplasm leads to the development of prometastatic reactions, also as well as specific organ also specific patient. Together with the systemic effect (e.g. paraneoplastic sdr) the organ-specific response activated by the neoplasm leads to the development of prometastatic reactions, also as well as specific organ also patient specific. This fact, suggested by studies performed on the healthy hepatic parenchyma of patients with CRC by biopsies performed during resection of the primary tumor, has highlighted prognostic implications on the development of metastases. In any case, it always remains to be considered that the liver, often the site of pre-existing chronic pathological alterations, is in close connection with other organs with which both in physiological and pathological conditions there is an exchange of informations and which is also of interest in the phenomenon of prometastatic reactions. Hence the discovery of the existence of portal vein-driven LPR stimulating factors from visceral fat, the hepatic artery-driven LPR-stimulationg factors and the existence of fundamental connection axes and crosstalks both in physiological conditions and in pathological conditions (e.g. neoplastic disease), which are obviously patient-specific and which lead to consider precision medicine approaches indispensable (liver-brain axis, hepato-pulmonary axis, liver-gut axis, liver-pancreas axis, liver-adipose axis, liver-spleen axis) [33,39].

Liver Disease and Liver Metastasis

During the metastasis process, the biological characteristics of the target organs are decisive. Generally, the target organs, already in the initial state of the disease, even before the onset of metastases, have already been affected by factors deriving from the primary tumor. Furthermore, the metastatic microenvironment does not depend only on the anatomy and biology of the target organ but also on the pathophysiological phenomena altered by the products of neoplastic cells or by pre-existing conditions. Numerous studies have evaluated the implications of a pre-existing liver disease or chronic inflammatory condition on the evolution of the development of metastases with sometimes conflicting results [40-44]. The coexistence of a pre-existing inflammatory activation, the presence of a subversion of the parenchymal structure, an alteration of the extracellular matrix, the activation of stellate and kupffer cells and the condition of oxidative stress that is created are phenomena that are recognized responsible in the promote metastasis [1,45-48].

Impact of Invasive Procedures

It should not be forgotten that all invasive procedures, from biopsy to determine the histology of the disease to resective surgical or ablative treatment, have local and systemic effects to consider. In addition to the well-known procedural complications (from bleeding to anastomotic dehiscence, etc.) the evoked inflammatory stimulus, dissemination caused by manipulation, wound healing and tissue repair phenomena and the immune response to stress have repercussions on progression and metastasis. The biopsy or surgical act, however, implies a manipulation of the microenvironment which, as is known, is able to influence the behavior of the neoplasm, possibly increasing local immunosuppression. The development of the inflammatory stimulus through the release of cytokines, chemokines and growth factor (e.g. VEGF) is part of the phenomena that promote progression and migration. At the same time, endothelial-mesenchymal plasticity is also activated, which promotes the migratory attitude of tumor cells. Invasive surgical procedures have a potential impact on primary tumor growth and metastasis [49]. Even non-invasive manipulation of the primary tumor mass has been shown to be able to determine the increase in circulating cancer cells [50,51].

Surgical procedures can exert effects also on secondary lesion by recruitment of neutrophils that induces metastatic progression, eliciting systemic factors promoting angiogenesis and proliferation, modifying the inhibitory control exerted by the primary tumor enhancing the metastatic progression [52-57]. Remodulation of the pre and prometastatic microenvironment of distant organs is also related to the hypoxic phenomena that are created following surgery on the primitive and to the phenomena of ischemia/ reperfusion injury that derive from some passages of the liver surgery techniques [58,59].

Treatments for Liver Metastasis

In recent years the therapy of liver metastases has achieved results of great interest thanks to the multidisciplinary approach. Collegial collaboration between surgeon, oncologist, molecular biologist, radiologist and gastroenterologist, allows for each patient a diagnostic and therapeutic itinarary and this improves the care. The approach to secondary neoplastic localization at the hepatic level has undergone a substantial evolution over 70 years, thanks to the development of techniques and knowledge and combined strategies that have contributed to modifying the perception of the extent of the disease and the result to be pursued. If the neoplastic disease is considered systemic much earlier, on the other hand, the objective of reducing the neoplastic mass is of main interest and the dogmas of the past on the non-resectability of liver metastases of some tumors (e.g. breast and stomach) have lapsed. While beneficial role of liver metastasectomy for Colorectal Cancer (CRC), Neuroendocrine Tumor (NET) origin and more recently for Gastrointestinal Stromal Tumours (GIST) and sarcomas is well established [59- 61] also liver metastasis from other tumors are now considered for resection. The possibility of resection for all the other non-colorectal, non-neuroendocrine and non-sarcoma has been object of several studies with increasing frequency and with adequate operative outcomes. Five-year survival rates following liver resection for non-traditional metastases have varied widely in the literature (19-57%), with the two largest series reporting 31% and 36%, respectively [62-66].

A multicenter study conducted on 203 patients who underwent liver resection between 1990 and 2013 in three centers (Mount Sinai, New York and Universiitary Hospital of Geneva and Zurich) for liver metastases of non-colorectal, non-neuroendocrine, Non-Sarcomatose and Non-Ovarian Origins (NCNSO) showed the benefit on survival generally comparable to that obtained for colorectal tumours by defining liver resection as an appropriate treatment for all these patients. Importantly, these results suggested that liver resection for NCNSO can offer a 5-year survival rate of 48% comparable to colorectal metastases [67-69] in selected cases identifying some prognostic factors:

a. metastases >35 mm were associated with lower survival in gastrointestinal tumors,
b. age > 60 years was associated with longer survival in patients with metastasis from breast cancers,
c. age > 60 years is associated with higher recurrence rate in patients with metastasis from “others” origin [69].

Breast Cancer Liver Metastasis

Recent studies have shown a positive role in liver resection for breast metastases in cases of absence of extrahepatic disease, with an improvement in overall survival and disease free survival. Patients with hepatic involvement have always shown a poor prognosis and historically have never been candidates for resective interventions, even if technically feasible, based on the systemic disease [70]. The introduction of new chemotherapy drugs improved survival and changed the approach, making hepatic resection considerable and liver resection has shown to be cost-effective instead of chemotherapy alone especially in ER positive tumors or when new agents were used [71]. Normally the percentage of patients with metastases confined to the liver represents 10% of patients with secondaryism. The OS reports an increase of 24 months for patients undergoing liver resection + CT compared to CT alone in two large European and US retrospective studies in disagreement with the study of the Memorial Sloan Kettering in which, however, the inclusion criteria were less restrictive than the first two and also included ablations as a treatment for liver metastases and not just surgical resection [72-77]. Favorable prognostic factors are the response to pre-hepatectomy chemotherapy, nodal status of the primary breast tumor, limited hepatic disease with fewer lesions, limited to one lobe, and hormone receptor status, and timing of metastasectomy (after 12 months or more), probably representing a disease stability due to systemic therapy [78].

Gastric Cancer Liver Metastasis

Given the greater aggressiveness compared to colorectal cancers, the presence of metastases has historically led only to systemic treatment, since the disease being considered as advanced and therefore not susceptible to surgical treatment. Numerous studies have instead highlighted the possibility of benefiting from surgical treatment on liver metastases also in this case, with rigorous selective criteria. The Guidelines Committee of the Japan Gastric Cancer Association suggests liver resection in the presence of resectable metastases from gastric cancer [79]. Several studies published since 2000 have emphasized the indication to resection for hepatic metastasis from gastric cancer highlighting an improvement in survival and defining a series of favorable and unfavorable prognostic factors suggested for the correct indications [80-82]. Hence, prognostic evaluation is

crucial to identify the suitable candidates for radical surgery from those who will not benefit from surgery. For the metachronous disease, Tiberio GA et al. [83,84] demonstrated that T4 gastric cancer, the presence of lymph node metastases, grade 3 GC were all negative prognostic factors. Also, Takemura et al. [85] reported the overall 5-year survival rate of 37% and the MST of 34 months in 64 patients achieved macroscopically complete (R0 or R1 resections.). So many factors have been defined; for primary tumors, favorable prognostic factor are: no serosal invasion, lower T stage, no lymphatic or venous invasion. For liver metastasis, favorable prognostic factors are unilobar involvment, solitary or less than 3 metastatic lesions, a diameter of greater lesion ≤ 5 cm, metachronous metastasis instead of synchronous. Moreover, from the general point of view they are to be considered prognostically favorable: absence of peritoneal metastasis, negative margin (R0), D2 lymphadenectomy, neoadiuvant therapy, adiuvant chemotherapy, response to chemotherapy, lower CEA and CA 19.9 levels, HER2-positive tumours treated with transtuzumab [84].

Making Resectable What is Not Resectable

The evolution of the concept of resectability has considerably expanded the indications from the point of view of the type of neoplasm, also involving many non-colorectal, non-sarcoma, non-neuroendocrine tumors. At the same time, the technical resectability criteria have evolved, giving prevalence to the concept of R0 and the use of all the usable tools necessary to achieve this purpose together with the preservation of the indispensable portion of residual parenchyma. Very complex resective techniques have developed in the last decade, starting from the renewed interest in a technique already described in the past, the **ERAT** (ex vivo liver resection followed by liver autotrasplantation) which theoretically allows a large number of contemporary hepatic resections also for lesions with extremely difficult localizations and with heroic vascular reconstructions to come to **ALPPS** (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) that with a two-stage intervention and exploiting the regenerative characteristic of the hepatic parenchyma is a very important surgical evolution of the almost routine interventional portal embolization before hepatectomy [86-88]. ALPPS has demonstrated to accelerate liver regeneration allowing the major resection after a median of 9 days, expanding resectability.

This technique was soon followed by many variations on the theme aimed at solving in a personalized way the specific problems or ineligibility to the procedure such as:

- Tourniquet ligation instead of transection **ALTPS** (Associating liver tourniquet ligation and portal vein ligation for staged hepatectomy);
- Radiofrequency ablation instead of transection **RALPPS** (Radiofrequency assisted liver partition with portal vein ligation for staged hepatectomy);
- PVE instead of portal vein ligation **Hybrid ALPPS** (Hybrid between ALPPS and portal vein embolization);
- Intraoperative PVE through a mesenteric catheter instead of portal vein ligation **Mini ALPPS** (Minimization of stage 1 ALPPS by endovascular embolization);
- Incomplete instead of complete transection **Partial ALPPS** Limited or partial transection of the parenchymal instead of complete transection [89-95].

Two other new techniques always with the intention of making resectable a disease initially unresectable by increasing the portion of the liver residue are: **Radiation lobectomy** and **Liver vein deprivation**.

In the first case, a standard treatment with non-selective embolization with Yttrio 90 is applied to a lobe, inducing atrophy and controlateral hypertophy. In the second case, in addition to the classic PVE, the outflow into the hepatic vein is also occluded, this to obviate the paraphysiological increase in arterial flow that follows the PVE which instead with this technique is reduced as a result of the occlusion also of the venous outflow [89].

Making transplantable what is not trasplantable

Liver Transplantation (LT) for irresectable colorectal liver metastases (i-CRLM) has long been ruled out because of poor short- and long-term results. After an initial expansion of the transplantability criteria between the 80s and 90s also for liver metastases, however, these indications had been abandoned for years due to the results in terms of survival. Since 2006 the concept of of transplant therapeutic possibilities has returned in vogue with promising results. The paradigm of intrasplantability for neoplastic disease has been overcome with the advent of a new real discipline: transplant oncology. For years now, the transplantability criteria include secondary neuroendocrine liver disease [96-98]. Also in 2013, a study at Oslo University Hospital showed good results obtained from transplant patients for unresectable metastases from colorectal cancer. However, the prosecution of this futuristic path had to be confronted immediately with the scarcity of available organs and the problems of mortality on the list and prioritysization [99]. To overcome these problems also of an ethical nature the Oslo group reported on 1 patient with i-CRLM, who underwent a combined segmental LT using a discarded small left lateral split liver graft from a deceased donor and a 2-stage hepatectomy following the ALPPS concept (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy). This novel strategy was described as the ‘‘**RAPID concept**’’ (resection and partial liver segment 2-3 transplantation with delayed total hepatectomy). After left hepatectomy, the small left lateral split graft was implanted

according to the APOLT technique (auxiliary partial orthotopic liver transplantation), and the right Portal Vein (PV) was ligated to induce hypertrophy. On Postoperative Day (POD) 23, when the graft reached a volume of almost 700 mL, the hepatectomy was completed [100,101].

In light of the lack of transplantable organs, the use of left lateral grafts for CRLM would mean denying a child or small recipient the chance for LT. Additional problems in this context are mainly posed by poor availability of splitable organs and many logistic problems, such as CT scheduling. A solution to these problems could be Living Donor Liver Transplantation (LDLT) using the left lateral segments only [100, 102]. In 2020 a further interesting technique has been described: heterotopic transplantation of segment 2-3 in the splenic fossa and delayed hepatectomy after regeneration of the transplanted graft , removing the spleen and modulating the native portal flow (**RAVAS procedure**) which combines the use of auxiliary liver and heterotopic transplantation in a case of unresectable liver metastases from CRCs. In this case, moreover, the use of a split graft from a suboptimal DBD donor has guaranteed not to compete with other candidates on the waiting list [103].

Locoregional Therapies, Systemic Effects and Future Perspectives

Ablative locoregional therapy is a valid alternative for patients not eligible for liver resection, both therapeutic and palliative. They are mainly based on the mechanism of thermal tissue destruction at high temperatures (radiofrequency ablation, microwaves ablation) or at low temperatures (cryoablation) or in the case of HIFU on a mechanical basis at high intensity. Great interest, however, was aroused not only by their locoregional efficiency, but also by the ability to evoke systemic responses. In fact, they produce a localized damage that produces tissue necrosis that remains in situ and that provides a good source of antigens of tumor origin that modulate the immune system. In addition, thermal and more rarely mechanical damage determines the establishment of inflammatory phenomena with the release of mediators with heat shock proteins and DAMPs which in turn cause the recruitment and activation of immunity cells. These phenomena that occur promptly after treatment but that are not fleeting can contribute with local effect, to the elimination of the tumor but also with remote effects with the control of micrometastasis, undetectable but already present elsewhere through the so called ‘abscopal effect’ and helping to create a long-term antitumor immunological memory; this could pave the way for a relevant role of locoregional therapy in anticancer immunotherapy [104,105].

Some preclinical and clinical studies have shown that distant metastasis can be regulated by an abscopal effect induced by RFA, showing regression. In fact RFA at primary site is able to create a substantial in situ source of acute inflammatory signals and tumor antigens in the form of necrotic tumor cells and cellular debris which have the potential to generate systemic immunity [106]. As for the immunoediting hypothesis, if tumor progression occurs as the immune system becomes tolerized or immune-resistant or immune-resistant tumor variants evade immune detection, the inflammatory effects of RFA can break the cycle of immune evasion. RFA-induces changes in the immune contexture favoring Th1/CD8+ T cell activation within the tumor microenvironment, which is indicative of activation of the innate and/or adaptive immune system, and peripheral lymphoid organs contribute to improved local and systemic tumor control after surgical resection. These findings establish that pre-resectional RFA impacts both the priming and effector phases of tumor-specific adaptive immune responses that are operative when excisional surgery was performed.

The observed increase in CD8+ effector T cells at tumor sites is predicted to provide a therapeutic benefit given evidence that high CD8+ T cell infiltration is a positive prognostic indicator in patients with primary colorectal cancer and colorectal liver metastases [107,108]. Evidence that delayed growth at distant tumor sites depends on CD8+ T cells following pre-resectional RFA is further in line with clinical observations of systemic tumor control after RFA treatment in renal cell carcinoma and prostate cancer patients [109-111]. The immunostimulatory activity of RFA could be exploited clinically in a neoadjuvant setting prior to surgery in patients with high risk of local and distant recurrence
[106]. These discoveries could greatly expand the indications to locoregional ablative therapies and with their application on the site of the primary tumor they could also become strategies with neoadjuvant presurgical neoadjuvant intent.

Immunotherapies

Advances in immunotherapy and the understanding of the cellular and molecular processes underlying the advancement of neoplastic disease and the evolution into metastatic disease have begun to modify the dramatic survival curves of metastatic disease, as it has been for example in the therapy of melanoma and lung cancer; a big limit, however, remains the drug resistance. Similarly to what has already been used for hematological diseases, cell-based immunotherapy treatments are explored that exploit ex vivo expansion and then retransfused into the patient in the process of adoptive cell therapy. The knowledge of the different steps and the multiple cells involved has allowed studies about immunity modulation of the host at various levels: blocking the recruitment of prometastatic immune-cells (drugs inhibitors of CCL2 chemokines or bone marrow derived CCR2+ monocytes), neutralizing survival factors of pro-metastatic immune-cells (reducing the survival of neutrophils and macrophages by targeting regulatory molecules

of these cell groups) and reprogramming pro-metastatic immune cells by epigenetically modifying their pro-metastatic phenotype [112]. The development of these techniques and these drugs is very promising as it brings out new and multiple stages of therapeutic application in synergy with other therapies allowing to modulate in a favorable prognostic sense of the same immune system of the host whether it is to modulate the formation of pre or prometastatic niche or to modulate the response to metastatic colonies.

However, the sensitivity to immunotherapy of liver metastases turned out to be much lower than, for example, lung metastases. This fact seems to be correlated with the immunotolerance of the liver itself and with the systemic effect of suppression of immunity triggered by liver metastases through induction of cell death of CD8+ T cells (immune desert). Liver radiotherapy was found to reduce intrahepatic antigen-specific T cell apoptosis, reshaping the liver immune microenvironment and abolishing immunotherapy resistance induced by liver metastasis [113].

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