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Hepatic Cancer: Present Scenario, Treatment Options and Nursing Management

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With an expected incidence of more than 1 million cases by 2025, liver cancer remains a problem for world health. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for nearly 90% of cases. Hepatitis B and C virus infection, alcohol abuse, and smoking are the main risk factors for developing HCC. Furthermore, the molecular pathogenesis of HCC linked with non-alcoholic steatohepatitis is distinct. A quarter of all HCCs have potentially treatable mutations that have not yet been implemented in clinical practice. The current hurdle in diagnosis is the requirement for molecular data that necessitates tissue or liquid biopsies.

Keywords: Hepatic cáncer; Hepatocellular carcinoma; Hepatoblastome; Metastases; Treatment.

Hepatic tumors

In Europe, 4-17% of new cancer cases diagnosed in 2012 were liver cancers[1]. In Asia, for example, a total of 582,420 incident cases were recorded in the year 2012 and this incidence was not related to the degree of Development of the country[2]. It is predicted that if management strategies in these areas will continue to be stable, the number of new cancer cases in Asia will rise by 2020. Worldwide, the burden of cancer is rising, which means stimulating efforts to prevent these diseases and to finding alternative therapies in local advanced or metastatic disease cases.

Primary liver tumors

Primary liver cancer (PLC) is the eighth leading cause of death for women and the fifth leading cause for men worldwide, and it has increased during the past few decades[3]. According to estimates from 2000, liver cancer is still the eighth most prevalent malignancy in women and the fifth most common malignancy in males worldwide. An estimated 564,000 new cases, including 166,000 women and 398,000 men, are reported annually.

Primary liver cancer includes hepatocellular hepatocarcinoma (HCC),

intrahepatic cholangiocarcinoma (ICC) and some other extremely rare ones. The trends in incidence are very variable comparing the different countries and also change over the years. A recent prevalence study collecting data from more than 30 countries showed that the incidence of primary liver tumors was highest in eastern and south-eastern Asia (Japan, China and Singapore), whereas in south-western and northern European countries was lowest[4-5].

Hepatocellular carcinoma

Among all types of PLC the Hepatocellular carcinoma is the first in frequency, accounting for 80-90% of all malignant tumors[6-7]. Due to its link to the hepatitis B and C viruses, HCC is a serious health issue on the rise globally. The world trends are unevenly distributed, finding the highest incidence in eastern Asia, followed by middle Africa, South-East Asia and the Pacific Islands[3]. The ratio of incidence between males/females ranges from 4:1 to 1.3:1, but the reason is still unknown. Concerning age distribution, it also varies depending on the geographic situation.

In 80–90% of cases, HCC results from a chronic liver illness such as chronic hepatitis B virus infection (HBV), chronic hepatitis C virus infection (HCV), drinking alcohol, eating food tainted with aflatoxin, and other rare etiologies. All these chronic hepatitis conduce after many years of evolution to liver cirrhosis as a substrate of the HCC. Chronic HBV infection, which accounts for more than 50% of cases and is the primary risk factor in Eastern Asia, is the most common risk factor for hepatocellular carcinoma. According to reports, the prevalence of hepatocellular carcinoma rises with viral load and infection time[8]. Hepatocellular carcinoma HBV-related can also be easily prevented by vaccination, as was shown in a study carried out in Taiwan, which demonstrated a decrease in the incidence of new cases of HCC in new-born after the implementation a universal program of vaccination[9].

About 3-5 % of people with HCV cirrhosis develop hepatocellular cancer yearly. HCC is a complication of cirrhosis brought on by HCV, especially in the US, Europe, Australia, and Japan. Cirrhosis progresses from infection on average over 20 years. In people with chronic HBV, HCV, or both infections, alcohol has a synergistic effect that increases the risk of developing hepatocellular carcinoma. The mechanisms by which alcohol causes HCC are not already known. As stated before, there also other minority causes for developing a HCC as the hemochromatosis disease or exposure to Aflatoxin but both with low incidence rates[6].

Hepatocellular carcinomas can look different histologically. Hepatocellular carcinoma frequently arises in the liver of people with advanced chronic hepatitis, and the presence of fibrosis and inflammation is a common characteristic. Tumor cells can be difficult to distinguish from benign hepatocytes in well-differentiated tumours because they resemble them. The large tumour cells in poorly differentiated tumours exhibit considerable pleomorphism and bear little similarity to healthy hepatocytes. Occasionally, a characteristic of tumour cells that helps with classification is the formation of intracellular bile. Hepatocellular carcinomas are characterised by an absence of intracellular mucus and a sinusoidal growth pattern. Hepatocellular carcinoma has two distinct subtypes: sclerosing hepatocellular carcinoma and fibrolamellar carcinoma (FL- HCC). When young patients are free of structural cirrhosis, the fibrolamellar variety naturally develops[10]. According to estimates, it accounts for 0.85 to 16 percent of all conventional hepatocellular carcinomas (HCC).

The tumors are solid and frequently contain a central fibrous scar, but it only occurs in less than 5% of the cases. Long-term survival of this subtype of HCC is significantly better than classical HCC. Survival 1, 3, and 5 years after liver transplantation ranged from 63 to 100 %, 43 to 75 %, and 29 to 55 %. However, disease recurrence after complete surgical resection of the FL-HCC is high in this patient population ranging from33–100 %.

Intrahepatic Cholangiocarcinoma

Cholangiocarcinoma (CC) is a tumor that growing from the biliary epithelium. Its frequency within the PLC is very limited, ranging from about 10-15% of the total tumors[6]. The spectrum of Cholangiocarcinoma includes intrahepatic, perihilar and extrahepatic tumors, which have a different epidemiology and therapeutic approaches. As with HCC the highest incidence rates of CC are found in northeast Thailand[11]. It seems to be well established that the ethiology of CC is highly

related to a situation of chronic inflammation. There are some entities as primary sclerosing cholangitis (PSC), choledochal cysts, *Opisthorchis viverrini* infection, hepatolithiasis or biliary papillomatosis, which present a strong association with the development of a CC[12].

Microscopically these tumors present themselves firm because of their prominent desmoplastic stroma. The most common microscopic pattern is a well to moderately differentiated adenocarcinoma forming small tubular glands and duct-like structures. This tumor has aggressive biology, and the prognosis is normally poor even in cases where a surgical resection is possible[13]. MRI or CT-scan often diagnoses CC, however the PET-CT scan present an accurate sensibility in the screening of lymph node metastases and extrahepatic disease, which would play an important role in the staging and therapy[14].

Hepatoblastome

It is the most common PLC in young children, accounting for over 50% the total. It is made up of tissue that resembles bile duct cells, adult liver cells, or foetal liver cells. Children with liver cancer may have alpha-fetoprotein (AFP), which is used as a biomarker to assist diagnose the condition[15]. Pathologically the tumors are often unique with a surrounding normal structure of the liver. It spreads in the regional nodes but also can produce metastasis in the lung, adrenal gland and bone.

Others: sarcoma, primary hepatic lymphoma

These are extremely rare tumors. An extremely rare form of lymphoproliferative cancer is primary hepatic lymphoma. It only accounts for 0.016 percent of all non-Hodgkin illness cases and 0.4 percent of all extranodal non-Hodgkin lymphoma cases. Primary hepatic sarcomas are also extremely unusual, as only 20-30 cases per year are reported in the literature[6]. Microscopically the most frequent pattern is angiosarcoma, which grows by extending along pre-exisiting vascular channels in the liver.

Secondary liver tumors

Liver is the most common site of metastatic disease at most becoming from the gastrointestinal tract, lung or neuroendocrine tumors. The following subsections would detail the different types of secondary tumors.

Liver metastasis of neuroendocrine tumors

Neuroendocrine tumors (NT) produce liver metastasis in 75% of the cases and can result in an extensive liver disease without finding the primary tumor[16]. From an embryological point of view, NT are derived from the embryonic neural crest, and their typical feature is to have the capacity to secrete hormones. The World Health Organization (WHO) classifies these tumors as well-differentiated vs poorly- differentiated NT[16].

Although the idea of differentiation and the grade of the tumours are related, there are notable distinctions between the two ideas. The degree to which neoplastic cells resemble their non-neoplastic counterparts is referred to as differentiation. Grade, however, describes the tumor's innate biologic aggressiveness. The percentage of tumour cells that are Ki-67 antigen positive per 10 high-powered microscope fields determines the grade of a tumour based on its rate of proliferation (hpf). Gastroenteropancreatic NET are considered low grade (G1) when < 2 mitoses / 10 hpf and <3% Ki67 index; intermediate grade (G2) 2-20 mitoses / 10 hpf or 3%-20% Ki67 index; high grade (G3) >20 mitoses / 10 hpf or >20% Ki67 index[17-18].

Patients with metastatic gastroenteropancreatic NET have a very diverse clinical history. Although they are mostly asymptomatic, they occasionally show symptoms due to hormone hypersecretion. Since they are more frequent, well-differentiated tumours account for 50% of all NETs in the gastrointestinal tract. Seventy three percent of individuals with hepatic metastases of neuroendocrine tumours on magnetic resonance imaging[19] and those with contrast enhancement on computer tomography exhibited the characteristic hypervascular pattern (CT). The most sensitive imaging is 18F-DOPA-PET/CT, which has shown to be superior to other traditional staging modalities and has high sensitivity and specificity in detecting NET lesions. They often present with a pattern of multiple liver small liver metastases. These normally have a more indolent course, as their growth rate is very low comparec to the colorectal-origin metastases (CRLM).

Colorectal liver metastases

Metastatic colorectal cancer (MCRC) represents the most common indication for liver resection, as colorectal cancer represents the 4th

most common cancer in western countries. Five-year survival after treatment ranges from 25%-37%[20-21] and more than 50% of the patients would present liver metastasis during the evolution of the disease[22] or other type of metastatic disease[23]. Until recently, patients with stage IV liver disease were relegated to palliative treatments or surgeries. However, since the last decade, it has been established that the first and foremost goal of Oncological surgery is to provide local control of the disease and even to treat the local or peritoneal recurrence. Nowadays there is contraindication for re-do surgeries[24].

From a histological point of view, sometimes it is very difficult to differentiate a metastasis from a PLC. One of the most difficult ones is distinguishing an intrahepatic cholangiocarcinoma from metastatic adenocarcinoma. Some immunohistochemical stains can help, but the sensitivity is very low. Liver metastases from CCR are normally not unique and rarely metastasize to bile ducts nor grow as intrabiliary tumor.

Data concerning tumor growth is very complex, and different cell cascades and pathways are involved in this process[6]. The natural history of colorectal cancer starts with transforming a normal intestinal epithelial cell into a polypoid lesion. The process continues with the sequenced transformation from an adenoma to carcinoma as a conclusion of accumulated mutations. At least two well-described genetic pathways may lead to colorectal metastases.

Chromosomal instability is the most prevalent mechanism, which mediates up to 60% of carcinomas. This is due to aneuploidy, allelic loss of 18q, p53, APC, and the protooncogene K-Ras mutations[25]. The role of the gene APC in the pathogenic of colorectal cancer is well known, as 100% of the patients with familial adenomatous polyposis (FAP) would develop a colorectal cancer in their lifetime without a proper treatment. The second pathway is microsatellite instability, which supposes a mutation in DNA mismatch repair genes and affects about 5-6% of the patients who have non-hereditary colorectal cancer.

The further distant dissemination from the tumoral cells depends on many different molecular pathways and the interrelationship between these cells with the stroma (endothelial cells, fibroblasts, immune cells) as well as the angiogenesis process. The four phases of the colorectal metastatic spread in the liver are the liver-infiltrating malignant cell phase, the interlobular micrometastasis phase, the angiogenic micrometastasis phase, and the established hepatic metastasis phase.

It has been demonstrated that the hepatic sinusoidal immune system, which includes hepatic-specific natural killer cells (NK) (pit cells), Kupffer cells (KC), and hepatic endothelial cells (HEC), is crucial in defending the liver against colon cancer cells. Kupffer's cells (KC) are the hepatic macrophages that have a relevant capacity to arrest tumoral cells from the bloodstream and avoid their penetrance into the parenchyma. However, KCs may promote liver colonisation if their capacity for tumoricidal activity is exhausted by an overabundance of invading cells or if metastases have already developed[26]. Similar to this, sinusoidal endothelial cells may help tumour cells enter the liver tissue when cytokines are activated by causing them to express intercellular adhesion molecules, which would strengthen the tumour cells' adherence and retention in the liver[27-28].

After endothelial adhesion of the tumoral cells within the sinusoids, strong intercellular bonds allow cells to resist the attractive forces of plasmatic flow and circulating blood cells[29]. They are allowed to penetrate across the Disse space and achieve the hepatocyte cytoplasm[30]. The tumoral cells would cause micrometastases in the hepatic parenchyma, and could remain in a dormant state ("sleep metastases") for an unknown period. To conclude the establishment of liver metástasis, it is probable that these micrometastases will be reactivated after an unspecified period and will create macrometastases.

When metastatic colorectal cancer is treated with a combination of chemotherapy (5-FU, oxaliplatin, irinotecan) and antiangiogenic drugs median overall survivals now extend beyond 24 months[31]. At the diagnosis, one-third of patients have advanced-stage disease without the option of curative resection. After a surgical resection by relapse, the liver is normally the main affected organ[32]. That's why new therapies which target this potential recurrence have to be envisioned.

Treatment options of the hepatic tumors

Resection: surgical anatomy and technique

Liver resection is often the only potentially

curative technique in treating primary and secondary hepatic tumors. With the development of preoperative diagnostic techniques and the improvement of intra- and postoperative patient management, liver resections can currently be performed with low mortality and a relatively low rate of complications[33]. There are some general technical considerations concerning liver resections, which can be applied universally to safely perform a liver procedure no matter the underlying cause.

Classically the liver division was considered in two lobes anatomically separated for the falciform ligament[34]. In the last century, the hepatic division has evolved towards a functional division based on the vascular distribution of the portal and hepatic veins branches. In 1950s, two authors, Couinaud[35] and Healey[36] proposed a similar system, which divided the liver into two hemi-livers along the middle hepatic vein (corresponding to Cantlie line) and each of one consequently subdivided into four liver segments. Portal and hepatic vein segmentation (french segmentation) was preferred by Couinaud over the arteriobiliary segmentation described by Healey[37]. All studies agree about the division of the liver into two hemi-livers. When taking into account what are customarily called the main ramifications of the triad, most investigators further subdivide the two hemi-livers into two further parts each, leading to a quadripartition of the liver or sectors.

In 2000 at Brisbane Conference of the International Hepato-Pancreato-Biliary Association (I.H.P.B.A), the hepatic segmentation was reconsidered by introducing the term of "sectional anatomy", a unitary surgical nomenclature and an updated terminology of liver resections were unanimously recommended and currently the most used.

In the last decades, liver surgery indications have expanded due to technological and technical improvements. Within the hepatic resections, we distinguish between anatomic resections including, hemihepatectomy, segmentectomy/ bisegmentectomy, which are supposed to follow these pre-established liver segments or atypical resections, which do not follow it. Anatomic resections are often performed in case of large or deep tumors, while atypical resections are in those peripheral situated. Each patient would require a single strategy and a laparoscopic approach could be also assessed in selected patients[38]. In the last twenty years, the laparoscopic approach has gained in popularity, and currently, even major hepatic resections can be safely performed laparoscopically[39-40]. Concerning the surgical technique, there are plenty of different mechanisms for splitting the liver parenchyma, and there is different data on which of the mechanisms had demonstrated to be superior[41-42]. Classically it had been stated that the resection margin must be >1cm, but in the latest publications, no relationship exists between overall survival and the width of the resection margin[43-44].

Concerning the extension of the indications of liver resections, new techniques have been described lately. Adam et al. described first in 2000 a two-stage hepatectomy addressed to patients whose initially irresectable metastases are down-staged by neoadjuvant chemotherapy[45]. In 2006, the Associating Liver Partition and Portal vein ligation (ALPPS) procedure were also introduced by Schnitzbauer et al.[46] as an alternative to patients with bilobar metastases. Since then several groups have published their results presenting favourable surgical and oncological outcomes[47-48]. Hereafter we will detail the specific considerations of liver resection for each type of tumor:

Resection of primary liver tumors

HCC and intrahepatic cholangiocarcinoma are the most common causes of liver resection in PLC. Although cholangiocarcinoma having more aggressive biology than HCC, with an appropriate surgical approach can achieve a longer survival in its initial stadiums. Liver resection indications in patients with HCC depend on the staging. There are several staging systems for the HCC. The Barcelona Clinic Liver Cancer (BCLC) is the only system that links prognosis with treatment recommendations, and thereby the BCLC staging system has been proposed as a standard for the assessment of prognosis in Europe and the United States[49-50]. Liver resection is normally recommended in patients in stages 0-A with normal liver function (Child-pugh A, occasionally B) and no portal hypertension[51-52]. The rest of the patients may be candidates for liver transplantation, ablative techniques or systemic therapies. Different studies have compared surgery for HCC with ablative treatments such as RFA, and the results suggest

that patients from the surgery group may achieve a longer overall survival and lower recurrence[53-54].

Surgical resection by intrahepatic cholangiocarcinoma is only curative in a few cases, as the majority of the patients have a spreading disease at the moment of diagnostic and the tumor has aggressive biology. Only 30% of them are potentially resectable, and the surgery involves a major/ extended liver resection. Despite a curative resection, the 5-year survival rate ranges between 10-40%[6]. In the last decade, liver transplantation has been introduced as a reasonable curative approach in patients with intrahepatic cholangiocarcinoma after receiving a determined radio-chemotherapy and having responded to the therapy, but that is still controversial[55–58].

Resection of colorectal liver metastasis

MCRC is the most frequent indication of liver resection as 10-20% of the patients present synchronous liver metastases at the moment of diagnosis, and 20-30% develop metachronous liver metastases[44]. Surgical resection appears to be the option of choice with a well-demonstrated benefit regarding long-term survival in MCRC and perhaps in neuroendocrine tumors, but this statement is not so clear in other types of tumors[59].

Indications for liver resection by MCRC have been expanded in the last decades. Traditionally, extrahepatic disease and bilobar metastases were contraindications to performing an extended liver resection. Still, it is currently accepted that a R0 situation and potentially cure could be achieved by pulmonary colorectal metastases resection or even by peritoneal carcinomatosis[23, 32, 60].

Currently, the possibility of a redo surgery or repeat hepatectomy by recurrent disease is a reasonable alternative, and several studies have published favourable long-term outcomes[61]. Lee H. et al. describe a 5-year disease-free survival (DFS) of more than 40% after secondary hepatectomy for recurrent CRLM, however, the recurrence rate was significantly higher compared with the first surgery[62]. In addition, each redo surgery adds a risk of complication when the surgery is not addressed to selected patients. In a nordish cohort of patients, the possibility of a liver transplant for patients with CRLM has also demonstrated favourable long-term outcomes when the patients fulfil the following premises: diameter of the largest CLM <55 mm, interval >2 years between colorectal and transplant operations, pre-LT carcinoembryonic antigen level <80 ng/ml, and responsive or stable disease under chemotherapy[63]. Therefore, in patients who would not be candidates for surgical treatments, other therapeutic options have to be envisioned, such as ablation.

Ablation of liver tumors

In the last 10-20 years, many ablative treatments for liver tumors have been described as an alternative to liver resection. As stated above, most patients whose liver function may be compromised by a liver resection would benefit from a minimally invasive approach and would thus avoid liver impairment. These patients are generally not surgical candidates due to their inability to tolerate general anaesthesia or widespread metastatic disease. Radiofrequency (RFA) and microwave ablation (MWA) are all ablative therapies based on thermal tumour damage and have emerged in the last years as promising techniques for tumor ablation[64-65].

Radiofrequency ablation (RFA)

In RFA, which involves the placement of one or more electrodes directly into the centre of the tumour, heat is produced by applying a high-frequency alternating current. Biological cells are sensitive to temperature[66]. This leads to thermal coagulation and protein denaturation of the plasmatic membrane, nucleic acids, and thus tumour destruction. Temperature rises to 60-100ºC to produce the expected necrosis effect. It's interesting to note_that temperatures beyond 100°C are less efficient because the desiccation that occurs at these temperatures, which manifests as water vapour and burnt tissue, increases the tissue impedance and so prevents further electrical conduction through the remaining tissue[67]. There have been described three zones of action depending on the circumferential distance from the tip: a central one, which undergoes ablation-induced coagulative necrosis (temperature around 60ºC), a peripheral zone of sublethal hyperthermia and the surrounding healthy tissue.

At this point, it is important to remark on the importance of the size of the ablation target to achieve an optimal treatment, which is one of the greatest limitations of the RFA. RFA is normally delivered by applying needle electrodes. The danger of exceeding the deadly energy

threshold rises with distance from the source due to the rapid radial reduction in the quantity of heat transferred to tissue (by a factor of roughly d2)[68]. In fact, in a recent meta-analysis evaluating the contributing factors of recurrence after RF ablation, the multivariate analyses showed that the tumor size > 3cm was an independent factor of greater recurrence[69]. Therefore, this approach would need several eclectrodes to correctly ablate a tumor > 3 cm.

Another limitation of the RFA is the so-called "heat sink effect", which means that when RFA is delivered close to a large vessel it produces a refrigerating effect and dissipates part of the heat, decreasing the ablative impact on the target tissue. It has been described in RFA suboptimal outcomes in those tumors situated near the main portal, hepatic veins or main bile ducts[69]. However, those are undesirable locations for a surgical resection and performing RFA.

Microwave thermal ablation (MWA)

MWA is also a thermal ablation technique which uses electromagnetic radiation to achieve tumor death with frequencies ranging between 915-2450 MHz. Dielectric hysteresis is used in microwave ablation to generate heat. When tissues are heated to deadly temperatures by an applied electromagnetic field, typically at 900-2500 MHz[70], tissue damage occurs. The fluctuating electric field forces tissue's polar molecules, mostly H_2O, to constantly realign, raising their kinetic energy and the tissue's temperature. Clinical studies are scarce as MWA is a relatively new technique and the greatest experience has been reported in Japan and China. Shibata et al. reported in a comparative cohort between RFA and MWA no differences in recurrence or in complication rates[71]. MWA has been proposed to decrease the "heat sink effect", but to date, there is not enough available data to support this theory. However, some groups defend a longer overall survival in the patients treated with MWA vs RFA[72]. On the contrary, other authors have drawn our attention to a potential higher rate of complications of the RFA compared to MWA when applied in peribiliary location[73].

Role of the oncology nurse

In the Asia-Pacific region, oncology nurses have two key chances to influence the incidence and treatment of hepatic cancer. It would be optimal if national oncology nursing associations formally sponsored both possibilities, pushing these interventions through consensus panel and cooperation with health ministries. Speciality oncology nurses use advocacy and education in their interventions.

Firstly is the availability of extensive public education. This should emphasise the value of immunizations in preventing HCC, the risks associated with intravenous drug use, and the significance of all-encompassing safety measures. To educate the public about the HBV vaccination prevention plan for probable HCC, oncology nurses can do it independently or collobrate with other healthcare professionals and educators. Across the Asia-Pacific, oncology nurses may launch a nationwide education campaign to raise awareness of this possibly curable illness and encourage preventive habits. Additionally, oncology nurses may instruct nursing students and generalist nurses who provide community health services. For elected or appointed authorities to advocate for increased resources (financial and human) to carry out outreach vaccination campaigns in remote areas.

Secondly, as it relates to HCC, oncology nurses who work in treatment settings play a crucial advocacy role. It is crucial to advocate for the inclusion of palliative care early on in the patient's experience when preparing for and to care for patients with HCC. For HCC patients and their carers, proficiency in managing symptoms (such as pain, exhaustion, anorexia, and gastrointestinal distress) and improving quality of life is crucial. When a patient's functional level is impaired by growing debility and symptom distress is prevalent, families also need instructions related to home care. Additionally necessary is the provision of emotional support for family caregivers who take on the majority of a loved one's care while remaining apart from the oncology team.

CONCLUSIONS

Although hepatic tumor information has not yet impacted clinical practice or trial design, it has improved our understanding of the molecular aetiology and heterogeneity of the disease. This gap will be filled by developing data connecting molecular subtypes with treatment actions. The growing capacity to categorise tumours via

liquid biopsies or other methods will provide a foundation for incorporating our molecular understanding of the illness into treatment choices as technology advances. Additionally, by identifying the mechanisms underlying resistance to present treatments, this data may pave the way for individualised healthcare that is catered to the needs of each patient. Oncology nurses in the Asia-Pacific region may be able to share "Best Practices" for treating this important group of patients with oncology nurses in other parts of the world. To do this, it is essential to improve public awareness, professional awareness, public education, symptom management skills, and research initiatives. In the end, transferring tumour biology into the clinic will keep patients' outcomes from declining.

Conflict of Interest

There is no conflict of interest

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REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *Eur J Cancer*, 49: 1374–1403 (2013).
2. Mohammadian M, Soroush A, Mohammadian-Hafshejani A, et al. Incidence and Mortality of Liver Cancer and Their Relationship with Development in Asia. *Asian Pac J Cancer Prev,* 17: 2041–7 (2016)
3. Bosch FX, Ribes J, Díaz M, et al. Primary liver cancer: Worldwide incidence and trends. In: *Gastroenterology*, pp. S5–S16 (2004)
4. Petrick JL, Braunlin M, Laversanne M, et al. International trends in liver cancer incidence, overall and by histologic subtype. *Int J cáncer,* 1978-2007 (2016).
5. Zhang Y, Ren J-S, Shi J-F, et al. International trends in primary liver cancer incidence from 1973 to 2007. *BMC Cancer,* 15: 94 (2015)
6. Clavien P-A. Malignant Liver Tumors: Current and Emerging Therapies. 3rd. Oxford: Wiley-Blackwell, (2010)
7. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*, 362: 1907–17. (2003)
8. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet,* 379: 1245–1255 (2012)
9. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*, 336: 1855–9 (1997)
10. Kassahun WT. Contemporary management of fibrolamellar hepatocellular carcinoma: diagnosis, treatment, outcome, prognostic factors, and recent developments. *World J Surg Oncol,*14: 151 (2016)
11. Sriraj P, Boonmars T, Aukkanimart R, et al. A combination of liver fluke infection and traditional northeastern Thai foods associated with cholangiocarcinoma development. *Parasitol Res,* 115: 3843–3852 (2016)
12. Clavien P-A, Baillie J. Diseases of the Gallbladder and Bile Ducts: Diagnosis and treatment. 2nd ed. Blackwell, (2006)
13. Yusoff AR, Razak MMA, Yoong BK, et al. Survival analysis of cholangiocarcinoma: a 10-year experience in Malaysia. *World J Gastroenterol,* 18: 458–65 (2012)
14. Petrowsky H, Wildbrett P, Husarik DB, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. *J Hepatol*, 45: 43–50 (2006)
15. Ruys AT, Groot Koerkamp B, Wiggers JK, et al. Prognostic biomarkers in patients with resected cholangiocarcinoma: a systematic review and meta- analysis. *Ann Surg Oncol*, 21: 487–500 (2014)
16. Martínez DTE, Sánchez-Chica PA, Del Valle Loarte P, et al. Primary Hepatic Lymphoma: the Importance of Liver Biopsy. *J Gastrointest Cancer*, 1–3 (2016)
17. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*, 39: 707–712 (2010)
18. Schiesser M, Veit-Haibach P, Muller MK, et al. Value of combined 6- [18F] fluorodihydroxyphenylalanine PET/CT for imaging of neuroendocrine tumours. *Br J Surg*, 97: 691–7 (2010)
19. Dromain C, de Baere T, Baudin E, et al. MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *AJR Am J Roentgenol*, 180: 121–8 (2003)
20. Charpentier KP. Irreversible electroporation for the ablation of liver tumors: are we there yet? *Arch Surg*, 147: 1053–61 (2012)
21. Primrose JN. Surgery for colorectal liver metastases. *Br J Cancer*, 102: 1313–8 (2010)
22. Silberhumer GR, Paty PB, Denton B, et al. Long-term oncologic outcomes for simultaneous resection of synchronous metastatic liver and primary colorectal cancer. *Surgery*, 160: 67–73

(2016)
23. Piso P, Arnold D, Glockzin G. Challenges in the multidisciplinary management of stage IV colon and rectal cancer. *Expert Rev Gastroenterol Hepatol*, 9: 317–26 (2015)
24. Sugarbaker PH. Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer. *World J Gastroenterol*, 20: 9286–91 (2014)
25. Paschos KA, Majeed AW, Bird NC. Natural history of hepatic metastases from colorectal cancer - pathobiological pathways with clinical significance. *World J Gastroenterol*, 20: 3719 (2014)
26. Bayón LG, Izquierdo MA, Sirovich I, et al. Role of Kupffer cells in arresting circulating tumor cells and controlling metastatic growth in the liver. *Hepatology,* 23: 1224–31 (1996)
27. Gangopadhyay A, Lazure DA, Thomas P. Adhesion of colorectal carcinoma cells to the endothelium is mediated by cytokines from CEA stimulated Kupffer cells. *Clin Exp Metastasis,* 16: 703–12 (1998)
28. Braet F, Nagatsuma K, Saito M, et al. The hepatic sinusoidal endothelial lining and colorectal liver metastases. *World J Gastroenterol*, 13: 821–5 (2007)
29. Haier J, Nicolson GL. The role of tumor cell adhesion as an important factor in formation of distant colorectal metastasis. *Dis Colon Rectum,* 44: 876–84 (2001)
30. Shimizu S, Yamada N, Sawada T, et al. Ultrastructure of early phase hepatic metastasis of human colon carcinoma cells with special reference to desmosomal junctions with hepatocytes. *Pathol Int*, 50: 953–9 (2000)
31. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol,* 14: 1208–1215 (2013)
32. Kianmanesh R, Scaringi S, Sabate J-M, et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. *Ann Surg*, 245: 597–603 (2007)
33. Clavien P-A, Petrowsky H, DeOliveira ML, et al. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med*, 356: 1545–1559 (2007)
34. Rouvière H, Delmas A, Götzens García V, et al. Anatomía humana: descriptiva, topográfica y funcional. Masson, (2005)
35. Couinaud C. Liver lobes and segments: notes on the anatomical architecture and surgery of the liver. *Presse Med,* 62: 709–712 (1954)
36. Healey JE, Schroy PC. Anatomy of the biliary ducts within the human liver; analysis of the prevailing pattern of branchings and the major variations of the biliary ducts. *AMA Arch Surg*, 66: 599–616 (1953)
37. Couinaud C. Liver anatomy: portal (and suprahepatic) or biliary segmentation. *Dig Surg*, 16: 459–67 (1999)
38. Wei M, He Y, Wang J, et al. Laparoscopic versus Open Hepatectomy with or without Synchronous Colectomy for Colorectal Liver Metastasis: A Meta- Analysis. *PLoS One,* 9: e87461 (2014)
39. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for Laparoscopic Liver Resection. *Ann Surg*, 261: 619–629 (2015)
40. Ciria R, Cherqui D, Geller DA, et al. Comparative Short-term Benefits of Laparoscopic Liver Resection. *Ann Surg,* 263: 761–777 (2016)
41. Rahbari NN, Elbers H, Koch M, et al. Randomized clinical trial of stapler versus clamp-crushing transection in elective liver resection. *Br J Surg,* 101: 200– 7 (2014)
42. Lesurtel M, Selzner M, Petrowsky H, et al. How should transection of the liver be performed?: a prospective randomized study in 100 consecutive patients: comparing four different transection strategies. *Ann Surg*, 242: 814–22, NaN-3 (2005)
43. Figueras J, Burdio F, Ramos E, et al. Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. Evidences from 663 liver resections. *Ann Oncol*, 18: 1190–5 (2007)
44. Hallet J, Sa Cunha A, Adam R, et al. Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg*, 103: 1366– 1376 (2016)
45. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg*, 232: 777–85 (2000)
46. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg*, 255: 405–14 (2012)
47. Linecker M, Stavrou GA, Oldhafer KJ, et al. The ALPPS Risk Score. *Ann Surg,* 264: 763–771 (2016)
48. Petrowsky H, Györi G, de Oliveira M, et al. Is Partial-ALPPS Safer Than ALPPS? A Single-center Experience. *Ann Surg*, 261: e90–e92

(2015)
49. Clavien P-A, Lesurtel M, Bossuyt PMM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol*, 13: e11-22 (2012)
50. Lin S, Hoffmann K, Schemmer P. Treatment of Hepatocellular Carcinoma: A Systematic Review. *Liver cáncer*, 1: 144–158 (2012)
51. Berzigotti A, Reig M, Abraldes JG, et al. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. *Hepatology*, 61: 526–36 (2015)
52. Berzigotti A, Reig M, Abraldes JG, et al. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: A systematic review and meta-analysis. *Hepatology,* 61: 526–536 (2015)
53. Park EK, Kim HJ, Kim CY, et al. A comparison between surgical resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. *Ann Surg Treat Res*, 87: 72–80 (2014)
54. Liu P-H, Hsu C-Y, Hsia C-Y, et al. Surgical Resection Versus Radiofrequency Ablation for Single Hepatocellular Carcinoma d" 2 cm in a Propensity Score Model. *Ann Surg*, 263: 538–545 (2016)
55. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg*, 242: 451-8-61 (2005)
56. Robles R, Figueras J, Turrión VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg,* 239: 265–71 (2004)
57. Rosen CB, Heimbach JK, Gores GJ. Surgery for cholangiocarcinoma: the role of liver transplantation. *HPB (Oxford),* 10: 186–9 (2008)
58. Mansour JC, Aloia TA, Crane CH, et al. Hilar Cholangiocarcinoma: expert consensus statement. *HPB (Oxford),* 17: 691–9 (2015)
59. Rees M, Tekkis PP, Welsh FKS, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg*, 247: 125–135 (2008)
60. Lemmens VE, Klaver YL, Verwaal VJ, et al. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J cáncer*, 128: 2717–25 (2011)
61. Nanji S, Tsang ME, Wei X, et al. Outcomes after repeat hepatic resection for recurrent metastatic colorectal cancer: a population-based study. *Am J Surg,* (2016)
62. Lee H, Choi SH, Cho YB, et al. Repeat hepatic resection in patients with colorectal liver metastases. *World J Gastroenterol*, 21: 2124–30 (2015)
63. Hagness M, Foss A, Line P-D, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg*, 257: 800–6 (2013)
64. Gnerlich JL, Ritter JH, Linehan DC, et al. Saline-linked surface radiofrequency ablation: a safe and effective method of surface ablation of hepatic metastatic colorectal cancer. *Ann Surg,* 250: 96–102 (2009)
65. Guenette JP, Dupuy DE. Radiofrequency ablation of colorectal hepatic metastases. *J Surg Oncol,* 102: 978–87 (2010)
66. Davalos R V, Rubinsky B, Mir LM. Theoretical analysis of the thermal effects during in vivo tissue electroporation. *Bioelectrochemistry,* 61: 99–107 (2003)
67. Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer,* 14: 199–208 (2014)
68. Seror O. Ablative therapies: Advantages and disadvantages of radiofrequency, cryotherapy, microwave and electroporation methods, or how to choose the right method for an individual patient? *Diagn Interv Imaging*, 96: 617–24 (2015)
69. Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg* , 242: 158–71 (2005)
70. Lubner MG, Brace CL, Hinshaw JL, et al. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol*, 21: S192-203 (2010)
71. Shibata T, Iimuro Y, Yamamoto Y, et al. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology,* 223: 331–7 (2002)
72. Correa-Gallego C, Fong Y, Gonen M, et al. A Retrospective Comparison of Microwave Ablation vs. Radiofrequency Ablation for Colorectal Cancer Hepatic Metastases. *Ann Surg Oncol,* 21: 4278–4283 (2014)
73. Van Tilborg AAJM, Scheffer HJ, de Jong MC, et al. MWA Versus RFA for Perivascular and Peribiliary CRLM: A Retrospective Patient- and Lesion-Based Analysis of Two Historical Cohorts. *Cardiovasc Intervent Radiol,* 39: 1438-1446 (2016)