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Review article

Liver tumors

Liver transplantation in metastatic liver tumors

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As transplant medicine has evolved in recent decades so too have the indications for liver transplantation (LT). Active or suspected malignancy has stopped being considered as a contraindication for organ transplantation, and nowadays LT plays a major role in the treatment strategies of liver malignancy, specially primary, but also metastatic. It offers excellent long-term outcomes for certain patients with neuroendocrine tumors liver metastases (NETLMs) and carefully selected patients with colorectal cancer liver metastases (CRLMs), who undergo neoadjuvant chemotherapy. Optimal patient selection has become the key issue to achieve the best possible outcomes and to deal with the alleviating shortage of organs. The recent tendency to incorporate markers of tumor biology into selection criteria, rather than simply focusing on tumor size and number, has led to further extension of indications for LT in patients with liver malignancy. This review article focuses on the current place of liver transplantation in the treatment strategy for patients with metastatic/secondary liver tumors.

Key words: liver transplantation, liver metastases, neuroendocrine tumor, colon cancer

Introduction

The idea of liver transplantation (LTx) as a method of treatment of unresectable tumor metastases limited only to this organ has been considered for several decades. However, due to significantly worse results, overall survival and high recurrence rates, LTs were initially abandoned [1–4]. At the turn of the century, however, the subject of liver transplantation as an effective "intent to cure" multiple metastases of neuroendocrine tumors to the liver (NELM) returned. The proven effectiveness of this procedure has even been reflected in Polish diagnostic and therapeutic recommendations for neuroendocrine tumors of the digestive system [5]. On the other hand, unresectable colon cancer metastases to the liver in the last 20 years of the 20th century were a contraindication to liver transplantation due to the described 5-year survival rate <20% [6, 7]. In 2006, recruitment for the SECA I study was launched in Norway to assess the effectiveness of orthotopic liver transplantation as a treatment for unresectable metastases of colorectal cancer to this organ in the current era of possible neo- and adjuvant therapies, various immunosuppression regimens and appropriate selection of recipients. Initial results showed overall survival of 60% [8]. Currently, about 20 clinical trials are being conducted worldwide to assess the effectiveness of treatment of unresectable metastases of colorectal cancer to the liver with orthotopic liver transplantation from a deceased donor, a fragment of a liver from a living donor and advanced surgical techniques: RAPID (resection and partial liver segment 2/3 transplantation with delayed total hepatectomy) and RAVAS (heterotopic transplantation of segments 2/3 using the splenic vein and artery after splenectomy and with delayed total hepatectomy), and the initial results are promising [9–11]. Currently, there is no trend to extend the indications for liver transplantation to other types of secondary, unresectable liver malignancies. Currently, research is focused on developing detailed recommendations regarding the selection of patients, organs and supportive

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therapies in order to obtain the overall survival values of patients after LTx due to unresectable cancer metastases similar to that in patients without cancer and the longest possible time without recurrence [12].

Transplant oncology

The transplant community has adopted a general guideline that survival at 5 years after liver transplantation by at least 50% of recipients justifies the use of expanded criteria organs (ECD). This principle applies both to transplants from living donors and from donors after brain death with maintained circulation and after cardiac arrest (DCD). From an oncological point of view, removal of the liver, extrahepatic bile ducts, and regional lymph nodes followed by transplantation would theoretically provide the best oncological eradication of primary and secondary hepatobiliary tumors. However, two main issues limit the possibility of using this method as the first line of treatment and the general acceptance of such a procedure. First, in most regions of the world, organ shortage limits the number of transplants and thus exposes waiting list cancer recipients to the progression of the above-mentioned cancer. Secondly, the benefits and risks of transplantation treatment should always be weighed in terms of patient survival, graft survival, the need for lifelong immunosuppression and the risk of recurrence of the underlying disease in immunocompromised patients.

Generally, there are two oncological indications for LT: primary (HCC and CCC according to the Mayo protocol) and secondary (discussed in this review) liver malignancy. Hepatocellular carcinoma (HCC), the most prevalent primary hepatic malignancy, represents 30% of indications for OLT in the United States since 2008 [13], with 5-year tumor recurrence-free survival rates (65–81%) comparable to those for general indications for end-stage liver disease (71–81%). Currently, only two indications for liver transplantation in the case of metastatic cancer are considered – neuroendocrine tumors (neuroendocrine liver metastases – NELM) and colorectal cancer (colorectal liver metastases – CLRM) [14]. LTx is an accepted definitive treatment for NELM as long as the primary NET has been resected and in the absence of more widespread disease. According to a recent systematic review, patients with NELM undergoing LTx provided 5-year overall survival rates between 49% and 97.2% and 5-year disease-free survival rates between 30% and 86.9% [14]. LTx results for CLRM have been discouraging so far. Moris et al. analyzed the data of 66 CLRM patients treated by LTx from 1972 to 2016 and described in 11 studies. Authors noted 1-, 3-, and 5-year overall survival of 85.2%, 48%, and 34.6%, respectively. Recurrence following LTx was very high as 66.7% (n = 44/66) patients recurred and 1-year DFS was only 38.9% [15]. However, according to a recent systematic review, patients with CLRM undergoing LTx provided 5-year overall survival rates between 50% and 83% and 5-year disease-free survival rates reaches 38% [16].

First time used by Hibi in 2017[17] the term of a new multidisciplinary branch of medicine, which is transplant oncology, should be introduced. It is a new concept including many disciplines of transplantation medicine and oncology, which aims to broaden the scope of treatment and research on cancer of the liver and bile ducts. Liver transplantation (LTx) in the case of primary and secondary malignant tumors of the liver and biliary tract is only part of this concept, and the whole critical elements of oncological transplantation are: the use of transplantation techniques in oncological surgery to extend the boundaries of conventional resection and the bridge connecting cancer and transplantation immunology, thus paving the way for a new anti-cancer strategy and genomic research platform based on new insights into cancer immunogenomics. This concept is intended to illustrate this new field of transplantation oncology and to highlight the importance of convening all relevant experts in the field of transplantation medicine and oncology, including transplant and hepatobiliary surgeons, medical oncologists and radiation therapists, hepatologists and gastroenterologists, immunologists, etc. to maximize care and cure cancer patients. In their concept, the authors emphasize the role of the four pillars of the new concept [18]: "The era of transplant oncology has just begun, and we are witnessing a paradigm shift in the treatment and research into hepatobiliary cancer. The 4 pillars of transplant oncology are:

1. evolution of multidisciplinary cancer care by integrating LT,
2. extending the limit of safe hepatobiliary resections by applying transplantation techniques to cancer surgery,
3. elucidation of self and nonself recognition system by linking tumor and transplant immunology, and
4. exploration of biomechanism of disease through genomic studies."

LTx for NELM – introduction

Neuroendocrine tumors/neoplasms (NETs/NENs) are a very heterogenous group of lesions including carcinoid, glucagonoma, gastrinoma, somatostatinoma, insulinoma, VIP-oma, ACTH-oma, pheochromocytoma and paraganglioma [19]. They originate from endocrine organs, the nervous system (peptidergic neurons) or from neuroendocrine cells of the diffuse endocrine system (DES) diffused throughout the whole body. Currently, The Surveillance, Epidemiology and End Results (SEER) program from US [20] states, that the incidence of NETs/NENs is estimated at 35 cases per 100,000 individuals per year.

Of all neuroendocrine neoplasms, about 70% are gastroenteropancreatic neuroendocrine neoplasms (GEP NENs), constituting only 2% of all gastrointestinal neoplasms, while most of them have blood drainage to the portal system and thus the possibility of metastases to the liver [21]. Among GEP-NENs, nearly half are intestinal and one third pancreatic. Among intestinal NENs only one fifth are hormone secreting. Out of pancreatic NENs only 10–30% are functional [22]. A majority of the NENs are non-functional indicating lack of symptoms

of hormonal hypersecretion thus making diagnosis difficult [23]. Although NETs are relatively rare, slow-growing tumors, once they begin to metastasize, the liver is the most commonly affected organ (40–93%, mean over 50%) after lungs and bones [10, 24]. Especially GEP-NENs metastasize to the liver with up to 77% of patients developing neuroendocrine liver metastases (NELM) in their lifetime [25]. The appearance of NELM is a confirmed negative prognostic factor for long-term survival [26].

The classification of neuroendocrine neoplasms according to the WHO 2019 and AJCC 2017 distinguishes 4 subtypes of NETs/NENs depending on proliferation index Ki-67%: NET G1, NET G2, NET G3 and NEC(-ancer) [27, 28]. Only patients with unresectable NET G1, G2 metastases are considered as potential liver recipients for transplantation [29].

Careful selection of patients with advanced NETs for transplantation involves the use of high-quality imaging strategies to accurately depict disease burden, with an emphasis not only on distribution diseases within the liver, but also possible extrahepatic deposits, such that may prevent the patient from qualifying for a transplant. Morphological and functional imaging methods play an important role in the assessment of NETs and their metastases. Three growth types of NELM were identified radiologically and have relevance to prognosis and treatment options: single metastasis (type I), isolated metastatic bulk accompanied by smaller deposits (type II) and disseminated metastatic spread (type III) [30]. Since most NELMs are hypervascular lesions, computed tomography (CT) must take into account the phases of the hepatic artery [31]. In addition, diffusion-weighted magnetic resonance imaging (DW-MRI) should be systematically performed in any NELM assessment as it has the highest specificity of all MRI phases, even in tumors <1 cm [32]. Functional imaging with positron emission tomography (PET) 68-gallium radiolabeled DOTA peptides in association with CT represent gold standard, because it can detect morphological changes imaging modalities cannot, as well as those that have not been identified by somatostatin receptor scintigraphy [22, 33]. ^{68}Ga-DOTA PET/CT imaging detects NELM with high sensitivity between 82–100% and a specificity of 67–100%. And detects extrahepatic diseases with 85–100% sensitivity and specificity 67–90% [22]. In fact, the main advantage of ^{68}Ga-DOTA PET/CT in the condition for surgical selection is its ability to identify extrahepatic disease and thus change clinical strategies, which is especially important when considering multivisceral transplantation [34, 35]. In addition to detailed radiological imaging of the disease state, the patient's functional status and significant comorbidities should also be assessed general condition of patients qualified for transplantation.

In conclusion, the radiological evaluation of the disease should include computed tomography (hepatic artery phase, best three-phase), MRI (especially DW-MRI), somatostatin receptor scintigraphy (in the presence of receptors) and if available, ^{68}Ga-DOTA PET/CT. The latter is essential in patients under liver transplant consideration because it presents the best opportunity to reveal extrahepatic disease that could preclude transplantation.

Selection criteria for LTx for NELM

Most of the authors from several studies agree with Mazzaferro that meeting the Milan criteria by the liver recipient provides the longest overall and disease-free survival. The Milan group reported 5-year overall and disease-free survival of 97% and 89%, respectively, with their patient selection criteria (tab. I) [19, 36]. However, among 280 patients with NELMs, only 88 patients (31%) were on the waiting list for LTx, while 42 patients (15%) underwent OLT [26, 36]. In another report, a subgroup analysis the ELTR study in patients undergoing LTx (n = 106) showed a 5-year overall survival of 59%. When the criteria of Milan was applied retrospectively, the calculated survival rate increased to 79%, but it referred only to 36% of the recipients. Although this study suggests an extension of the Milan criteria, G3 histology grade is considered a contraindication to LTx [37]. In the US, the current OPTN/UNOS OLT guidelines for NELM (tab. I) are mainly based on the Milan-NET Criteria with a few additional conditions (OPTN/UNOS Liver and Intestinal Organ Transplantation Committee) [38]:

Table I. Summary outcomes reported from selected series on LTx for NELMs

First author	Year of publ.	Incl. period	Country	Patients (n)	1-year OS	3-years OS	5-years OS	1-year DFS	3-years DFS	5-years DFS
Nguyen	2011	1988–2011	US	184	79.5%	61.4%	49.2%	–	–	–
Le Treut	2013	1982–2005	Europe	213	81%	65%	52%	65%	40%	30%
Nobel	2016	2002–2014	US	230	87%	69%	63%	–	–	–
Mazzaferro	2016	1995–onwards	Italy	42	–	–	97.2%	–	–	86.9%
Valvi	2021	1988–2018	US	206	89%	75.3%	65%	74.9%	55.7%	43.9%
Maspero	2022	1984–2019	Italy	48	–	98%	95.5%	–	84%	75%
Eshmuminov	2022	1988–2021	international	225	–	–	73%	–	–	64.2%

OS – overall survival; DFS – disease-free survival

Milan-NET selection criteria (2007, revised in 2016):

- low grade NET (G1-G2) confirmed on histology,
- portal drainage of the primary tumor,
- primary tumor and all deposits radically removed in a separate operation before consideration for transplant,
- metastatic liver involvement <50% of liver volume,
- stable disease or response to treatment for at least 6 months prior to listing,
- age under 60 years (relative criteria).

Summary of UNOS guidelines for LT in NELM:

- common criteria with Milan-NET,
- additional criteria:
  - unresectable liver metastasis,
  - radiographic characteristics of NELM,
  - negative metastatic workup by PET scan,
  - lack of extrahepatic tumor recurrence during the past 3 months,
  - the presence of positive findings for lymph node metastases by PET scan,
  - the finding should become negative for 6 months before re-listing,
  - the presence of extrahepatic solid organ metastases (i.e., lungs or bones),
  - the case will be permanently delisted.

Literature review

To date, several studies have been published on OLT in NELM, including registry reports, multicenter series, and single center prospective and retrospective series (tab. I). The largest series reported in 2013 is the ELTR retrospective analysis by Le Treut et al. [39], which identified 213 patients who received OLT between 1982 and 2009. Before LT, 83% of patients underwent surgical treatment with removal of the primary tumor (n – 158) or liver metastases (n – 58); these included 23 cases of severe liver failure after resection (10.8%). In addition, 161 (76%) patients received non-surgical treatment, including somatostatin analogues in 63 patients, and transarterial chemoembolization (TACE) in 76 patients. 90-day post-operative mortality was 10%; significant risk factors included early retransplantation, exenteration, splenectomy, surgery duration over 10 h, margin of R1/R2 resection, hepatomegaly and additional surgeries after LTx. Regarding survival, the median OS after OLT was 67 months, with 1-, 3- and 5-year overall survival rates of 81%, 65%, and respectively 52%. Disease-free survival rates over the same time intervals were respectively 65%, 40%, and 30%. This ELTR study also demonstrated improved 5-year overall survival over time, with rates of 46% for recipients transplanted before 2000 in comparison to 59% for LTx done after 2000, respectively.

A 2011 analysis of the United Network for Organ Sharing (UNOS) database by Nguyen et al. [40] covered 184 patients with NELM (treated in 1988–2011). Overall survival rates at 1, 3, and 5 years were 79.5%, 61.4%, and 49.2% respectively.

Retrospective registry analysis performed by Nobel and Goldberg was reported in 2016. Authors studied the variable use of MELD exception points in patients with NELM and their impact on treatment outcomes; they showed 1-, 3, and 5-year posttransplant patient survival rates among all transplant recipients with metastatic NETs, regardless of exception points, at 87% (79–92%), 69% (59–77%), and 63% (53–72%), respectively. These rates were significantly (11%!) lower than national posttransplant survival rates for all first-time transplant recipients (80% and 74% 3- and 5-year survival, respectively, for all transplant recipients) [41]. In 2016, Mazzaferro et al. [36] evaluated 280 NELM patients referred for LTx consideration – the only prospective study with clearly defined selection criteria comparing transplanted and non-transplanted groups occurred (Milan NET criteria). In the end, 88 qualified and 42 actually passed the LTx. 5-year and 10-year overall survival rates in the transplant and non-transplant groups were 97.2% and 88.8% *vs.* 50.9% and 22.4%. The frequency of recurrence at 5 years and 10 years were 13.1% and 13.1% in the transplant group compared to 83.5% and 89% in the non-transplant group.

In 2022 Maspero et al. published a retrospective analysis comparing survival and disease recurrence in NELM patients undergoing transplantation (n – 48) or liver resection (n – 56) treated at the same center in 1984–2019. Patients undergoing LTx had better long-term outcomes compared to resected patients: 5-year and 10-year OS rates of 95.5% and 93% *vs.* 90% and 75%, respectively; 5-year and 10-year DFS rates of 75% and 52% *vs*. 33% and 18%, respectively.

In the aforementioned Milan group study, there was also a different pattern of cancer recurrence in the treatment groups. Multi-site recurrence was more frequent in patients after LTx (48% *vs.* 12%), in patients after resections mainly in the liver (88% *vs.* 8%), and recipients after LTx had longer median time-to recurrence (6.5 years *vs.* 2 years) than those undergoing only liver resection [42].

Also in 2022, Eshmuminov et al. analyzed a data pool from 15 large international centers on their NELM patients treated with LTx or liver resection (LR). Study concern 455 patients with NELM who underwent LTx (n – 225) or liver resection (n – 230) between 1988 and 2021. Multivariable analysis revealed negative prognostic factors: G2-NELM and LT outside Milan criteria for transplanted patients, while G3-NELM for resected patients. Comparison results are: 73% 5-year OS after LT *vs*. 52.8% 5-year OS after LR and 64.2% DFS after LT *vs.* 14,2% DFS after LR [43].

A favorable LTx result for NELM can be achieved by appropriate risk stratification in tumor biology, burden of the NELM, R0 resection feasibility, patient performance status, and expected waiting time for LTx. Based on the analysis of prognostic factors, the following was reported:

- LTx should be reserved for G1 and G2 NELM only based on mitotic and proliferative index (e.g. Ki-67). A Ki-67 index over 10% has been considered a marker of poor prognosis,

- the Milan group suggested that only liver metastases from NETs with
- portal venous drainage should be considered for LTx,
- functional involvement of the liver parenchyma at a level of 50% has been suggested as a cut-off point in considering to transplant. However, due to the subjectivity of the assessment this should not be considered as an absolute contraindication,
- resection of the primary tumor prior to LTx is recommended in order to
- monitor NELM biological response,
- LTx with R1 or R2 margins is not recommended,
- evidence of extrahepatic spread is a contraindication to LTx,
- the correct LTx time remains debatable. Some authors have proposed 6 months as the waiting time for observation of biological behavior of the tumor,
- there is no consensus on the importance and reasonable cut-off age for LTx [44].

LTx for CRLM – introduction

According to Global Cancer Statistics 2020, colorectal cancer is the third most common cancer in the world's population (out of 36 malignancies in 185 countries) and the second, after lung cancer, with the highest mortality [45]. Over the last quarter of a century, the incidence of colorectal cancer has been increasing, especially in the group of young adults [46]. The 5-year survival rate of patients with colon cancer according to the CONCORD 2 study (1995–2009) was slightly over 60% in twelve Western European countries. In Poland, this rate was 50% in patients with colon cancer and 47% in patients with rectal cancer [47]. The most common malignancy in the liver is metastasis of colorectal cancer [48], which will occur in more than 40% of patients with a primary tumor in the colon [49]. Technically feasible radical liver resection, presents the best treatment option, offering long-term survival [50–52]. More and more advanced parenchyma-sparing techniques are being used, which increase the percentage of patients in whom radical resection is possible [53, 54]. Despite nearly 50% of patients with colorectal liver metastases have unresectable disease [55–57]. This leads to an extremely unfavorable situation, because the 5-year overall survival of patients with CLRM treated only with systemic therapies is less than 20% [58]. In addition, 40–75% of patients experience a recurrence of the malignancy after surgery [59, 60], with more than half the recurrences involving the liver [61, 62]. Despite repeated resections, the prognosis is poor and depends on hepatic failure due to subsequent progression and recurrence. During the initial qualification for LTx of patients with CRLM, in order to exclude extrahepatic lesions, it is mandatory to perform a 3-phase angioCT, MRI and PET-CT with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). However, due to the possible false-negative results of involvement of the lymph nodes of the hepatic lymph confluence (hepatoduodenal ligament) in imaging studies, it is recommended to take a frozen section sample of the above-mentioned lymph nodes [63]. PET-CT is a valuable tool in evaluating extrahepatic metastases. In addition, from the data, PET-CT can be estimated by the so-called defined metabolic tumor volume (MTV) as an enhancement volume that is equal to or greater than 40% of the normalized maximum uptake volume [64]. This helps to assess the biological aggressiveness of the tumor, and MTV seems to be an effective predictor of poor prognosis after LTx in patients with CLRM. Cumulative MTV of all liver lesions per patient below 70 cm^3 clearly differentiates between better and worse long-term survival [65].

Selection criteria for LTx for CRLM

The prerequisite for qualifying a patient with CLRM to LTx is that the primary lesion was radically removed in accordance with the standards of care. The foregoing selection process basically aims to identify patients with favorable tumor biology which is hard to define term. Tumor biological behaviour associated to an array of clinicopathological and molecular features/properties characterized by high variability among patients and types of cancer. After the analysis of the qualification process and the results of trials: SECA II, RAPID, Compagnons group and preliminary data from LDLT trials in North America centers, the factors associated with poor prognosis after LTx for CRLM were given and divided into 4 groups [66].

Group 1 – characteristics of the primary tumor: primary tumor on right side of large intestine, lymph node positive primary tumor, time interval between primary resection to liver transplantation <2 years, signet ring cell carcinoma, BRAF mutation. Group 2 – characteristics of liver metastases: largest lesion >5 cm in size (Fong score) or 5.5 cm (Oslo score), more than one lesion, synchronous metastases, progression of metastases during chemotherapy, metabolic tumor volume (MTV) >70 cm^3. Group 3 – disease extent: presence of extrahepatic disease. Group 4 – molecular biomarkers: carcinoembryonic antigen.

Most of these factors are reflected in the scales used to qualify patients with CLRM to LTX. Mainly, the five-stage Fong scale (Fong Clinical Risk Score – FCRS), which was created in 1999, originally to assess the risk of recurrence of colorectal cancer after resection, and the four-stage Oslo Score (2020), which is the esult of the experience of the Norwegian group in LTx patients with CLRM (SECA I and SECA II studies). The four-stage Oslo score with each criterion value 1: largest lesion diameter >5.5 cm, pre-transplant CEA level >80 lg/ml, progression on chemotherapy, time from resection of primary tumor to transplant <24 months. The five-stage Fong Clinical Risk Score with each criterion value 1: node positive primary, interval from diagnosis of primary to liver metastasis <12 months, >1 liver metastasis, pre-resection CEA level >200 lg/ml, maximal lesion diameter >5.0 cm. For both scales, selection based on a score of 0 to 2 has been associated with 5- year survival outcomes comparable to other indications for liver transplantation [67].

Table II. Summary outcomes reported from selected series on LTx for CRLMs

First author	Year of publ.	Incl. period	Country/city	Patients (n)	1-year OS	3-years OS	5-years OS	1-year DFS	3-years DFS	5-years DFS
Hoti	2008	? –1994	ELTR data	50	62%	–	18%	–	–	–
Hagness	2013	2006–2011	Norway	21	95%	68%	60%	35%	–	–
Toso	2017	1995–2015	Lisbon, Coimbra, Paris, Geneva	12	83%	62%	50%	56%	38%	38%
Dueland	2020	2012–2016	Norway	15	100%	83%	83%	53%	44%	35%

OS – overall survival; DFS – disease-free survival

Literature review

To date, preliminary and longer-term results of only three major considerate studies of the efficacy of LTx in patients with unresectable CLRM have been reported (tab. II).

- SECA I [68]: in period 2006-2011, included 21 patients, Oslo/Norway, results: OS – 1-year 95%, 3-years 68%, 5-years 60%, DFS – 1-year 35%, 2-years 0%, conclusion: LTx is feasible for patients with unresectable CLRM.
- SECA II [69]: in the period 2012-2016, included 15 patients, Oslo/Norway, results: OS – 1-year 100%, 3-years 83%, 5-years 83%, DFS – 1-year 53%, 2-years 44%, 3-years 35%, conclusion: more restrictive selection criteria improve outcomes.
- Compagnons Hepato-Bilaires [70]: included 12 patients, Lisbon/Coimbra/Paris/Geneva, results: OS – 1-year 83%, 3-years 62%, 5-years 50%, DFS – 1-year 56%, 2-years 38%, 3-years 38%.

As mentioned, several studies of the effectiveness of LT in patients with CRLM are currently in progress and the preliminary results are still 2–3 years away. These are prospective, randomized studies on deceased donor liver transplantation, LDLT and Rapid procedure [71].

Conclusions and recommendations

In conclusion for neuroendocrine neoplasms, unresectable NELM resistant to conventional therapy with no evidence of extrahepatic disease is an accepted indication for LTx. However, the recommendations of the working group from the ILTS Transplant Oncology Consensus Conference should be used [72]:

1. "LT should be considered as a potentially curable treatment option for selected patients with unresectable metastatic NET of midgut/hindgut origin confined to the liver (moderate level of evidence and strong recommendation).
2. Selection criteria should consider ^{68}Ga-DOTATATE, Ki-67, histology, site of origin, and a certain time interval of stable disease or good response to therapies (moderate level of evidence and strong recommendation).
3. LT for selected patients with metastatic NET confined to the liver as part of multimodality therapy should achieve comparable outcomes as LT for other diagnoses (moderate level of evidence and strong recommendation).
4. Everolimus has achieved improvement in progression-free survival in NET and should be considered as part of immunosuppression after LT for NETLM (low level of evidence and strong recommendation).
5. Late recurrences beyond 5 years after LT are not uncommon, necessitating long-term follow-up with annual imaging (moderate level of evidence and strong recommendation)."

In conclusion for CRLM, LTx is an exciting therapeutic option for patients with unresectable metastases to the liver from the large intestine, and ultimately it can also be used for selected resectable patients. Current evidence is limited, but many studies are ongoing, and it is likely this field will grow significantly over the next decade with increasing experience and knowledge about outcomes, selection criteria and prognostic factors becoming available.

For liver transplantation due to CRLM, Transplant Oncology working group's guidelines have also been developed to point the way to an optimal selection of patients for LT and prepare the ground for future basic and clinical research [70,72], so quoting:

1. "LT can be a viable option in highly selected patients with unresectable CRLM with only liver involvement (moderate level of evidence and moderate recommendation).
2. LT for CRLM with low Oslo score ≤2 (maximum tumor diameter ≤5.5cm, pretransplant carcinoembryonic antigen ≤ 80 µg/L, response to chemotherapy, time interval: diagnosis to LT ≥ 2 y) may improve the 5-year overall survival rates over those achieved with the current standard of care (moderate level of evidence and moderate recommendation).
3. Minimization of immunosuppression is recommended (low level of evidence and moderate recommendation).
4. Aggressive treatment of all posttransplant resectable recurrences is recommended (low level of evidence and moderate recommendation).
5. There is a need for an international registry to coordinate data collection and design further studies on LT for CRLM (moderate level of evidence and moderate recommendation)."

Various forms of liver transplantation (orthotopic, partial, living related, auxiliary – RAPID/RAVAS) are a challenge and con-

troversial (mainly ethical), but also potentially the most effective approach to cure patients with NELM or CRLM. Over time, we observe better patient selection (both in terms of transparency and stringency) and better immunosuppression strategies, which transfers to longer overall survival of patients and cancer recurrence-free survival. For patients with NELM, the role of neoadjuvant/adjuvant therapies in reducing post-transplant recurrence needs to be solved. For patients with CRLM, the completion of several ongoing prospective studies in 2–3 years will help to determine the effect of LTx compared to palliative chemotherapy, hepatic artery infusion (HAI) or other best possible therapy and the validity of the selection criteria.

Article information and declarations

Author contributions

Marcin Kotulski (70%) – concept of the study, review of the literature, writing and editing the manuscript.
Piotr Smoter (20%) – review of the literature, writing and editing the manuscript.
Tadeusz Wróblewski (5%) – review of the literature, writing and editing the manuscript.
Michał Grąt (5%) – review of the literature, writing and editing the manuscript.

Conflict of interest

None declared

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