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THE CHANGING LANDSCAPE OF TRANSPLANT ONCOLOGY: OPPORTUNITIES AND CHALLENGES

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Summary

Transplant oncology is a clinically focused field that aims to offer cancer patients treatment options beyond standard medical, surgical, and oncologic care. The primary drivers of transplant oncology include advancements in transplant surgery, the increased use of extended-criteria donors, shifts in the epidemiology of liver disease, and new insights into cancer biology and immunology mechanisms. While liver transplantation (LT) is the primary focus, transplant oncology covers all solid organ transplant (SOT) categories, including kidney, lung, heart, intestinal, and multivisceral transplants. Several reports and a few randomized clinical trials have demonstrated the potential benefits of transplant oncology if complex, well-coordinated, multidisciplinary treatment protocols are followed. However, the benefits of transplant oncology are challenged by concerns about resource allocation, ethical dilemmas in patient selection, and a thorough understanding of the complex relationship between cancer and the innate and adaptive immune systems. Further development of transplant oncology requires shifting the clinical focus from the donor-to-recipient dyad – where the chance of cure depends solely on donor graft availability – to a structured approach that addresses allocation policies, timely coordination of multidisciplinary interventions, technological advancements, and resilience from healthcare organizations, managers, and stakeholders. Ultimately, beyond resources, offering oncologic patients an alternative option through transplantation demands competency rooted in medical, bio-immunological, and surgical transplant care.

Key words: transplantation, oncology, patients, outcome, controversies

Abbreviations

CNI: calcineurin inhibitor
CRC: colorectal cancer
CSC: cancer stem cell
ECD: extended criteria donors
ELTR: European Liver Transplant Registry
EVR: everolimus
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HEHE: hepatic epithelioid hemangioendothelioma
HT: heart transplantation

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ISHLT: International Society for Heart and Lung Transplant Registry
KT: kidney transplantation
LT: liver transplantation
LuT: lung transplantation
MASLD: metabolic dysfunction-associated steatotic liver disease
mTOR: mammalian target of rapamycin
mTORi: mammalian target of rapamycin inhibitors
RCC: renal cell cancer
SOT: solid organ transplantation
UNOS: United Network for Organ Sharing

TRANSPLANT ONCOLOGY: THE BENEFITS

The term "transplant oncology" has gained prominence in the transplantation field recently, driven by clinical experiences that have expanded oncologic indications for liver transplantation (LT) [1,2]. The main factors advancing transplant oncology include the decreased impact of viral infections as reasons for LT [3], along with more frequent use of extended criteria donors (ECD) [4]. The notable shifts in the epidemiology of liver disease – due to the introduction of antiviral treatments for HCV [5] and the control of HBV replication [6] – as well as the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) [7], have changed the clinical demand for LT, even though the overall need for transplantation remains high [8].

Transplant oncology is not a new concept in medicine. The earliest cases of LT in the USA and Europe involved patients with extrahepatic biliary adenocarcinoma, advanced hepatocellular carcinoma (HCC) – formerly called hepatoma – and colorectal (CRC) liver metastases [9]. Even the first lung transplant was performed in 1963 on a patient with advanced lung cancer [9]. In its early days, due to poor initial results, transplantation was considered a last resort for incurable cases, and clinical selection focused on patients with advanced cancers deemed untreatable by standard surgery. The burden of surgery, the lack of suitable immunosuppressive options, and the high incidence of graft rejection, along with suboptimal intensive care, all contributed to the poor outcomes of these early attempts [9]. Fifty years after these initial experiences, the transplant community has embraced treating advanced malignancies with renewed interest, although it remains controversial and continues to be debated [1]. Transplant oncology presents clinical, ethical, and organizational challenges, requiring experience, dedication, and resilience to manage all issues related to its implementation in clinical practice. In this paper, we review the current advancements in transplant oncology in a narrative format and discuss the controversies surrounding its further expansion.

Liver transplantation

LT is the area that has seen the most extensive use of transplant oncology so far [2] (Fig. 1). This is because the liver is often affected by primary and secondary cancers [10], and HCC is a common complication of liver cirrhosis and an established indication for LT [11]. Central to these advancements has been the introduction of radiologic and surgical strategies to downstage liver tumors before LT [12], along with the recent development of immunotherapies [13]. Over the years, we have learned that liver grafts have an immune privilege compared to other solid organ transplants (SOTs) [14], allowing for reduced exposure to immunosuppressants when compared with kidney transplants (KTs) or heart transplants (HTs) [15]. Finally, we have expanded our understanding of the bio-immunologic mechanisms that drive cancer initiation, growth, and progression for numerous cancer types, including the liver [16-18].

Beyond CRC liver metastases, which have experienced the most significant growth within LT transplant oncology [19], neuroendocrine tumors [20], and cholangiocarcinoma [2] are increasingly being considered (Fig. 1). However, the landscape also includes, although sporadically, the incidental or intentional transplantation of patients with pancreatic neoplasm [21], gallbladder carcinoma [22], early gastric cancer [23], and sinonasal metastatic carcinoma [24]. Additionally, case reports of multi-organ transplantation in patients with liver failure and extrahepatic liver malignancies have been documented for breast cancer [25] and stage III lung cancer [26]. Vascular malignancies are a limited but definitive indication for LT [27]. Hepatic epithelioid hemangioendothelioma (HEHE), a rare vascular tumor, may have a clinical course similar to highly aggressive angiosarcoma [28]. Data from the United Network for Organ Sharing (UNOS) and a recent study from the European Liver Transplant Registry (ELTR) [29] demonstrated favorable survival outcomes, with 10-year overall survival rates of 74.4% [29]. A specific indication for LT includes pediatric liver malignancies [30]. Hepatoblastoma is the most common primary liver cancer in children, mainly treated with chemotherapy and liver resection. However, for tumors with extensive liver involvement – such as a centrally located tumor unsuitable for resection or involvement of the portal vein and hepatic vein – LT is indicated, with a long-term survival rate of 85%-90% (30). LT has also been performed for rare liver malignancies in infants, such as biliary embryonal rhabdomyosarcoma (31) and hepatic mesenchymal hamartoma [32] (Fig. 1).

Extra-hepatic transplantation

Although initially considered a contraindication, several scholars and scientific societies are redefining the indications for KT for patients with a history of renal cell cancer

(RCC) [33], as well as how to manage de novo or recurrent RCC after transplantation [34] (Fig. 1). Lung cancer accounts for 0.1% of the indications for lung transplantation (LuT) over the past two decades. However, contrary to usual exclusion criteria, the post-transplant survival rate for these patients is comparable to that of patients with non-cancerous diseases [35]. Moreover, LuT may provide a curative option for patients with bilateral lung cancer whose respiratory failure has progressed independently of cancer advancement [35]. Although controversial, HT may be an option for patients with cardiac cancer or malignancies involving the heart [36]. A recent study from the International Society for Heart and Lung Transplant (ISHLT) registry included 104 patients over 35 years and reported a median survival in the cancer cohort of 3.6 years [36]. Intestinal transplantation can be an option for patients with surgically untreatable pseudomyxoma peritonei [37] and desmoid tumors [38], and multivisceral transplantation has been reported for patients with advanced neuroendocrine tumors [39]. Finally, uterus transplantation can be a treatment option to restore fertility in female patients with a history of uterine cancer [40] (Fig. 1).

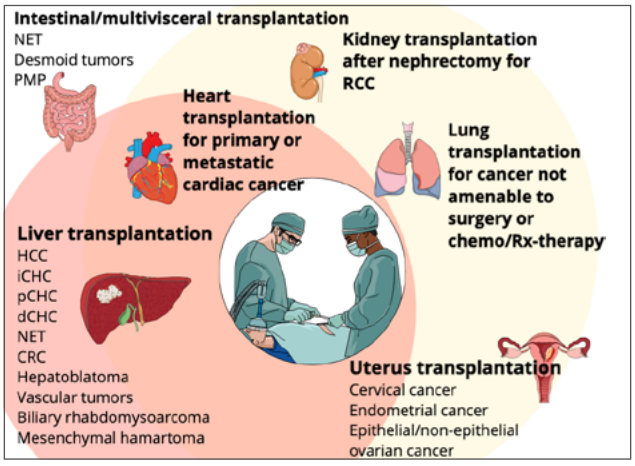

Figure 1. Although liver transplantation is the transplant oncology area that has received the most attention, several reports have been published on intestinal/multivisceral, kidney, lung, heart, and uterus transplantation for treating early or advanced malignancies (Based on references [10-40]).
CHC: cholangiocellular carcinoma; dCHC: distal CHC/biliary adenocarcinoma; iCHC: intrahepatic CHC; pCHC: peri-hilar CHC; CRC: colorectal cancer; HCC: hepatocellular carcinoma; NET: neuroendocrine tumor; PMP: pseudomyxoma peritonei.

TRANSPLANT ONCOLOGY: THE CHALLENGES

Implementing new medical practices typically requires a careful and structured approach to ensure patient safety and achieve optimal results. This includes thorough evaluation, pilot testing, and a gradual rollout with ongoing monitoring and assessment [41]. Significantly, new practices should be grounded in solid evidence and developed by a multidisciplinary team, considering patient preferences and potential barriers to adoption [41]. Nonetheless, the potential benefits of transplant oncology – such as offering patients a possible solution for otherwise untreatable conditions – and the high level of expertise in transplant surgery worldwide are fueling its growth within the transplant community, though not as extensively in routine cancer care [42]. Several authors have already suggested possible solutions to support further expansion of transplant oncology, mainly focusing on surgical and technological advancements [42] (Fig. 2).

Expansion of oncologic indications might harm non-oncologic waiting list candidates

One perceived obstacle to expanding oncologic indications in transplantation is the limited availability of grafts and their suboptimal viability [8] (Fig. 2). Furthermore, including more cancer patients on transplant waiting lists could worsen this shortage, leading to tough decisions and potentially affecting outcomes for patients with other conditions (i.e., the concept of harm to the waiting list) [43]. Especially in the field of liver disease, MASLD is estimated to impact up to 38% of the Western adult population, with 15-20% progressing to cirrhosis and a median age of 70 years [7]. MASLD has become the leading cause of liver transplants in the United States for women and those with HCC [7]. Additionally, MASLD is linked to increased risks of developing de novo diabetes mellitus, chronic kidney disease, sarcopenia, and extrahepatic cancers [7]. As a result, more complex MASLD patients are expected to receive transplants over the next two decades in the Western world [7]. Although not unique, one potential approach is to modify current graft allocation algorithms, shifting elderly and suboptimal donors to oncologic patients who could benefit significantly from organs with shorter expected lifespans compared to younger, optimal liver grafts [44]. A further strategy recently implemented to address potential harm caused by reallocating organs from decompensated liver disease patients to oncological indications is expanding the use of elderly donors [45] and dynamic perfusion techniques, i.e., machine perfusion, to rescue organs and reduce early allograft dysfunction (EAD) [46].

Patient selection

Careful patient selection is crucial for improving transplant oncology success and decreasing the risk of recurrence [42] (Fig. 2). However, when selecting patients, various factors

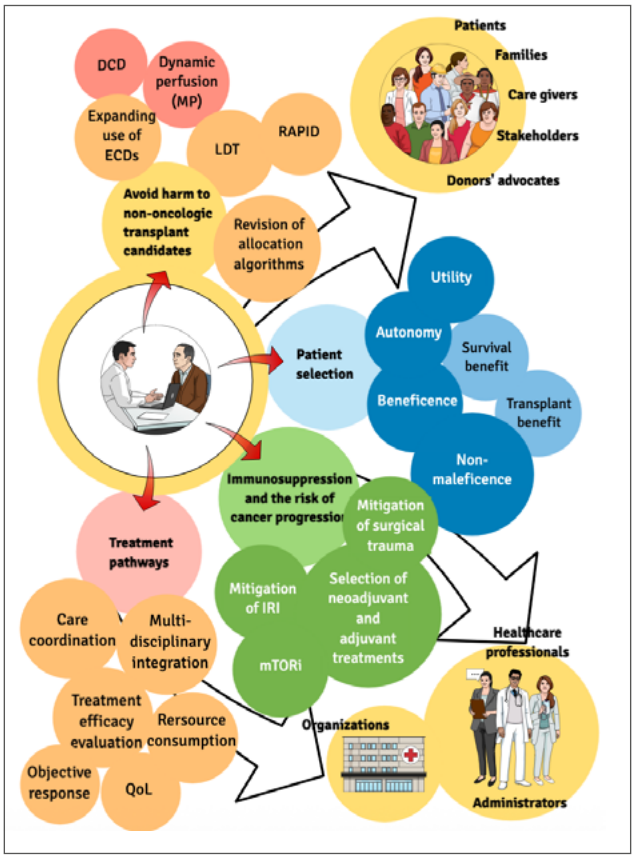

Figura 2. A visual overview of the challenges involved in refining and expanding transplant oncology. Four key areas require attention: preventing harm to non-oncologic transplant candidates, refining patient selection criteria, enhancing current immunosuppressive protocols by incorporating both immunosuppressive and non-immunosuppressive strategies, and streamlining treatment pathways. All these strategies require the participation of patients, caregivers, stakeholders, healthcare professionals, administrators, and organizations.
DCD: donors after circulatory death; ECD: extended criteria donors; IRI: ischemia-reperfusion injury; LDT, living donor transplantation; MP: machine perfusion; mTORi: mammalian target of rapamycin inhibitors; QoL: quality of life; RAPID: resection and partial liver segment 2-3 transplantation with delayed total hepatectomy.

may be considered depending on resource availability, disease epidemiology – which influences transplant demand – the status of the transplant waiting list, and the values of patients, their families, and the community [47]. The principles of autonomy, non-maleficence, beneficence, justice, utility, dignity, and honesty often conflict and must all be balanced by the healthcare team [47]. *Autonomy* is the patient's right to accept or refuse any treatment if they can make decisions independently and based on informed consent, rather than having a paternalistic decision made on their behalf by healthcare providers. Supporters of this view justify expanding transplant oncology indications based on individual patients' right to make their own decisions. *Non-maleficence* refers to the principle of not causing harm or, more accurately, no additional harm with the treatment being offered. Supporters of this approach consider transplant oncology therapies justified if they do not worsen the outcomes that patients would experience without that specific treatment. *Beneficence* implies that healthcare providers must offer benefits in the best interest of the individual patient after carefully weighing risks and benefits. Supporters of this approach justify transplant innovations based on evidence of a benefit for their patients. This benefit, however, may consist of a net survival advantage (i.e., an extension of the individual's anticipated lifespan) or a survival gain compared to alternative treatments (i.e., a transplant benefit) [48]. *Utility* involves the fair distribution of limited health resources within society and the allocation of treatments to those who need them (fairness and equality). Supporters of utility favor using grafts for patients with the best predictable outcomes. Lastly, *dignity and honesty* are the patient's rights to be treated with dignity and to receive truthful information without suppression of essential facts by healthcare providers [47]. Notably, although the patient's perspective must be prioritized, care providers, families, stakeholders, and communities should all be involved in the decision-making process [47]. Finally, the content of these principles is dynamic – they require constant adaptation to advancements in technology. Given the rapid pace of current technical and theoretical developments, providing patients with the most comprehensive information for independent decision-making can often be challenging, as it requires expertise and competency.

Immunosuppression and cancer

Another hesitation that has limited the growth of transplant oncology is the perceived risk that cancer patients face a higher chance of recurrence due to post-transplant immunosuppression [49] (Fig. 2). Although the immunosuppressive options for SOT recipients are stagnating, experimental and clinical research has expanded our understanding of the immunobiological mechanisms that promote cancer recurrence, progression, and metastasis [17,18]. Better profiling of cancer genomic and phenotypic characteristics is increasingly available in clinical practice and should be further integrated into the choice of the immunosuppressive regimen for transplant oncology patients. Some issues remain unresolved, such as determining the optimal duration of immunotherapies before transplantation and their limited implementation in the post-transplant course [50]. However, recent reports have demonstrated some survival advantages in selected types of recipients at experienced centers, with a 6-month progression-free survival rate of 56.8% and an allograft rejection rate of 25.8% [50].

Organization

One of the main challenges to the growth of transplant oncology is organizing multidisciplinary treatment pathways (Fig. 2). Based on LT experience, treating patients with advanced HCC requires coordinating multiple specialties and the timely integration of surgical, radiological, oncological, and immunological therapies [51]. Similarly, implementing transplantation for hilar cholangiocarcinoma according to the Mayo protocol, which includes external beam radiation, intraductal radiation, chemotherapy, laparoscopic staging, and living donor liver transplantation, demands complex and well-timed treatment [52]. The organization of similar protocols is expanding to LT for CRC [2] and LT for neuroendocrine metastases [20], where multimodal, neoadjuvant therapies are a crucial part of the treatment plans. In turn, this organization relies on the physical and cultural environment of the healthcare setting, as well as the experience and skills of the healthcare professionals involved.

SCOPE SHIFT IN TRANSPLANT ONCOLOGY COMPARED TO TRADITIONAL TRANSPLANTATION

A final aspect to consider regarding the expansion of transplant oncology is how its clinical applications have evolved in comparison to traditional SOT. Initially seen as either lifesaving or life-enhancing procedures, this distinction is not always relevant to transplant oncology, which has a much broader scope and purpose. Moreover, although transplant oncology is continually challenged by advances in immune-oncology, surgery, and interventional radiology, it relies on these fields to achieve its clinical goals and enhance its applications. Typical examples include LT for CRC metastases, which aims not only to overcome the limitations of current chemotherapy and surgical treatments but also to enable patients to tolerate additional treatments after tumor reduction – i.e., *converting* the tumor phenotype to a more treatable form [2,19]. The concept of *reconversion through transplantation* has already been explored and may seem contradictory to the traditional idea of transplantation as a destination therapy [25]. In this context, transplantation can be part of a planned therapeutic strategy to improve treatment effectiveness that would otherwise be unreachable or to achieve temporary objectives. Restoring liver function in the presence of multifocal metastatic involvement [25], transforming liver-dominant metastatic disease into a non-liver-dominant form, or enabling staged hepatectomy, such as in the resection and partial liver segment 2-3 transplantation with delayed total hepatectomy (RAPID) procedure [53], are notable examples of these approaches. In this regard, uterus transplantation after oncologic disease exemplifies transplant oncology procedures aimed at accomplishing temporary but meaningful goals for the recipient, such as otherwise unattainable pregnancy [40].

CONCLUSIONS

Translating transplant oncology into clinical practice requires a fundamental rethinking of most current treatment algorithms. Decades of clinical experience in transplantation have been based on the donor-to-recipient dyad, where the chance of cure has solely depended on the availability of donor grafts. Implementing and expanding transplant oncology demands a structured approach that addresses allocation policies, well-timed coordination of multidisciplinary interventions, cutting-edge technological advancements, and resilience from healthcare organizations, managers, and stakeholders. Finally, beyond resources, providing oncologic patients with an alternative option through transplantation requires expertise rooted in medical, bio-immunological, and surgical transplant care.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

EFK, PDS: conceptualized the study, made critical revisions; MG, AR: wrote the preliminary draft. All authors prepared the draft and approved the final version.

Ethical consideration

Not applicable.

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