Liver Transplant for Nonresectable Colorectal Cancer Liver Metastases in South Africa: A Single-Center Case Series

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Abstract

Objectives: **Publication in 2013 of the first Secondary Cancer cohort study returned attention to liver transplant for nonresectable colorectal cancer, demonstrating excellent outcomes for a procedure that was historically contraindicated. The Wits Donald Gordon Medical Centre in Johannesburg, South Africa, hosts the largest liver transplant program in sub-Saharan Africa. The persistent shortage of deceased donor organs in our setting has compelled us to innovate solutions unique to our context, which allows us to perform as many transplants as possible and maximize our resource utilization. Therefore, we initiated a research study to transplant organs in patients with nonresectable colorectal carcinoma with expanded criteria using marginal deceased donor organs that would otherwise have been discarded.**

Materials and Methods: **Institutional Review Board approval was obtained for this study. We used criteria from the 2013 Secondary Cancer cohort study to determine eligibility of patients with nonresectable colorectal carcinoma for liver transplant. Unlike the study from 2013, we utilized expanded criteria and marginal liver allografts for transplant.**

Results: **Five patients have undergone liver transplant for nonresectable colorectal carcinoma. At a median follow-up of 36 months (range, 10-52 months), 4 of the 5 (80%) patients are alive. The patient who died had progressive disease on chemotherapy pretransplant and was the only patient who tested positive for the Kirsten rat sarcoma viral oncogene homolog mutant. Recurrence occurred in all patients at a median time of 6 months after transplant (range, 3-13 months).**

Conclusions: **To our knowledge, this is the only published case series of patients undergoing liver transplant for nonresectable colorectal carcinoma in Africa and is internationally unique in its use of expanded criteria and marginal grafts for this type of transplant. Despite the use of such grafts in our recipients, thus far, these outcomes align with those of the 2013 Secondary Cancer cohort studies from Norway.**

Key words: *Chemotherapy, Norwegian Secondary Cancer study*

Introduction

Historically, liver transplant for colorectal metastases was abandoned as a therapeutic option after a series of inferior outcomes during the 1990s. At the time, most deaths resulted from perioperative complications and were not due to disease recurrence. However, over the past 2 decades, both the fields of liver transplant and oncology have evolved, and today, liver transplant is an established therapeutic option for primary carcinomas of the liver and liver metastases from neuroendocrine tumors. These primary liver carcinomas include hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, and hemangioendothelioma. Secondary carcinomas include metastases from neuroendocrine tumors.[1]

The recent expansion of oncological indications for liver transplant has been facilitated by an overall improvement in survival from liver transplant, improved diagnostic modalities to determine the extent of metastatic involvement of the liver and other organs, and improved chemotherapeutic agents that allow for effective multimodal treatment strategies to enhance patient survival.[1] By defining stringent inclusion criteria for transplant candidates with these types of cancers, a minimum 5-year

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survival rate of 60% is achievable. Arguably, this survival benchmark renders such transplants feasible and ethically justifiable but also requires careful consideration, given the local and regional circumstances of each transplant program.[2]

In 2013, results from the original Norwegian Secondary Cancer study (SECA-I) placed liver transplant for nonresectable colorectal carcinoma (NRCRC) back into the spotlight, challenging the transplant community to reconsider the exclusion of such patients from transplant.[3] The Norwegian SECA-I study capitalized on the unusual organ donor situation in Norway, where deceased donor (DD) organ supply exceeds demand. It was on this basis that surplus DD liver grafts were implanted into 21 patients with NRCRC who fulfilled specific inclusion criteria, although these criteria were relatively broad. After transplant, the SECA-I cohort demonstrated an overall 5-year survival rate of 60% after a median follow-up of 27 months (interquartile range, 8-60 months) compared with a 10% rate of 5-year survival for patients on palliative chemotherapy.

The findings of the SECA-I study provided a basis for the Norwegian team to refine the inclusion criteria for the second study (SECA-II), which has recently shown improved outcomes over SECA-I, with a 5-year survival rate of 83% after a median follow-up time of 36 months (interquartile range, 5-60 months). Both SECA studies reported disease recurrence after liver transplant; however, the rates of recurrence differed substantially. The SECA-I study demonstrated a recurrence rate of 90% in patients (19/21). With more stringent inclusion criteria, recurrence rate in the SECA-II cohort dropped to 33% (5/15). Most recurrences were resectable pulmonary metastases, and both SECA studies demonstrated disease-free survival after surgery for recurrent disease. Although the results of the SECA-I and SECA-II studies are promising, the consensus in the scientific community is that further studies in diverse patient cohorts are needed to validate these findings before endorsing NRCRC as an indication for liver transplant, particularly in transplants programs with DD organ shortages.[4]

Colorectal cancer (CRC) is one of the most common malignancies in high-income countries, and approximately half of those affected develop liver metastases. In sub-Saharan Africa, the incidence of CRC appears to be increasing, but the absence of population-based registries prevents us from establishing true incidence rates.[5,6] In South Africa, the most recent report from the pathology-based National Cancer Registry confirmed that CRC is the sixth most common malignancy in women and the fourth most common malignancy in men.[7] Approximately 20% of South Africans with CRC present with advanced disease, primarily in the form of colorectal liver metastases.[8] For patients with resectable colorectal liver metastases, complete resection of the liver metastases is the only treatment associated with long-term survival. Internationally, the 5-year survival rate for patients with liver resection is reported at 46% versus a 5-year survival rate of 6% without liver resection. Moreover, one-sixth of patients can expect 10-year survival after resection, if selected appropriately. In patients with NRCRC starting first-line chemotherapy, 5-year survival rate is 10%, and median survival after starting second-line chemotherapy is 10 to 12 months.[9]

In South Africa, outcomes of metastatic CRC are congruent with those reported internationally, with a 5-year survival rate after liver resection of 57%.[8] However, this survival rate was reported as a subset of a larger cohort in which only 23% of patients (n = 60) presented with resectable liver metastases. The remaining patients (77%; n = 203) presented with NRCRC and were treated with chemotherapy alone, and the 5-year survival rate was between 10% and 15%.[8] Hence, prognosis for patients with NRCRC is dismal, both locally and internationally.

The Transplant Unit at Wits Donald Gordon Medical Centre in Johannesburg, South Africa, was established in 2004 and has achieved acceptable outcomes over a relatively short time. The most recent annual report showed an overall unadjusted recipient survival rate at 1 year of 83% (95% CI, 74% to 89%) and at 3 years of 75% (95% CI, 65% to 83%). In contrast to the organ-replete milieu of the Norwegian SECA studies, severe organ shortages persist in South Africa, with lower DD rates than most other countries with transplant programs. To address organ shortages, our transplant unit performs split liver grafts whenever possible, and we have introduced an adult living donor liver transplant program that is still in its early stages. Despite organ shortages, two-thirds of our adults on the wait list are transplanted within 60 days of listing.[10] Although these numbers may seem counterintuitive, these results may be affected by the lack of access to

appropriate specialist care centers, the low referral rates for those with end-stage liver disease, and an overall relatively low number of transplants in South Africa. Although we perform liver transplant for the previously mentioned oncological indications, this report describes our first experience of liver transplant in a case series of South African patients with NRCRC.

In 2016, we were approached by a colleague with NRCRC who was eligible for liver transplant according to the SECA-I criteria. Given our pervasive DD organ shortage and the fact that NRCRC is not an established transplant indication, we approached our Institutional Review Board for permission to perform a transplant for this patient with one proviso: we would not compromise wait list status of patients with recognized indications for liver transplant. The only way we could achieve this would be to transplant a DD organ that would otherwise have been discarded. After extensive deliberation, our Institutional Review Board approved these transplants, with the conditions that the staged research study was subjected to careful oversight and that each recipient was fully aware of the organ allocation process.[11] We were permitted to undertake the first case (approval number M151137), and, after providing our results to the Institutional Review Board, we subsequently received permission to perform a further 4 cases, all of which are detailed in the present report. Given our outcomes, our Institutional Review Board approved this program as an ongoing research study in our Transplant Unit, the first of its kind in sub-Saharan Africa. Because this was a research project, patients were required to undergo a research information process and to provide research-related consent, over and above standard transplant consent procedures.

Materials and Methods

We used the SECA-I criteria to determine eligibility of patients with NRCRC: hepatic-only CRC metastases confirmed by magnetic resonance imaging, computed tomography scan, and fluorodeoxyglucose positron emission tomography scan; prior resection of the primary tumor; completion of, at least, first-line chemotherapy; and fulfillment of the standard criteria for liver transplant at our center. At the time of the transplant procedure, repeat computed tomography scans of chest and abdomen were performed to exclude interval development of extrahepatic malignant disease.

At the time of transplant, standard immunosuppression was administered and comprised intraoperative methylprednisolone and, from post-transplant day 1, combination oral prednisone, mycophenolate mofetil, and tacrolimus (targeted to levels 10-15 μmol/L, for the first 6 weeks after transplant). Tacrolimus was then substituted for everolimus (targeted to levels of 5-8 μmol/L), and oral corticosteroids were withdrawn within 6 months. Patients who received an ABO incompatible (ABOi) allograft additionally underwent a course of plasma exchange until the relevant isoagglutinin levels were less than a ratio of 1:4, and this was followed by 2 doses of rituximab, 1 week apart. The study protocol conformed to the ethical guidelines of the 2013 Declaration of Helsinki.

Results

Patient overview

Five patients who met the inclusion criteria underwent liver transplant for NRCRC in this series. An overview of patient demographics and clinical profiles can be found in Table 1. The median time from resection of the primary tumor to transplant was 14 months (interquartile range, 5-53 months). According to the TNM Classification of Malignant Tumors standard for stages of a primary tumor, 4 of the 5 patients had T3 tumors. One patient was staged as T0, after completion of first-line chemotherapy. In all 5 patients, the liver metastases were diagnosed at the same time as, or within 12 months of, the primary colorectal tumor, hence designated as synchronous lesions.

Donor overview

All of the liver allografts for this series were procured from deceased adult donors. No living donor allografts were used. South African has an "opt-in" policy for organ donation, and consent was obtained for the donor next-of-kin in all cases. All donors were diagnosed with brainstem death, as donation after circulatory death is not widely practiced in South Africa.

Clinical outcome

At a median follow-up of 38 months (range, 10-54 months), 4 of the 5 patients (80%) were alive (Figure 1).

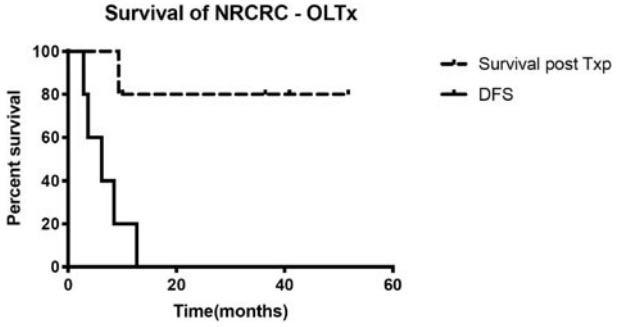
Table 1. Patient Demographics and Clinical Profile

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	62	67	36	59	35
Sex	Male	Male	Male	Male	Female
Primary tumor					
Location	Sigmoid	Rectum	Rectum	Colon	Sigmoid
TNM stage	T0, N0	T3, N0	T3, N0	T3, N1	T3, N2
Interval to transplant, mo	5	53	5	14	31
KRAS	Wild	Wild	Wild	Mutant	Wild
Chemotherapy					
1st line	FOLFOX	FOLFOX + Bev	FOLFOXIRI + Bev	FOLFOX	FOLFOX + Cetux
2nd line	FOLFIRI + Cetux	FOLFIRI + Bev	FOLFIRI + Cetux	FOLFIRI + Bev	Capecitabine + Cetux
3rd line		Capecitabine			
Response	Yes	Yes	Yes	No	Yes
CEA at transplant	14	356	1	4	8
Liver resection	No	No	No	Yes × 2	Yes × 2
RFA or SIRT		RFA and SIRT			RFA
Hepatic tumor					
No. of lesions	15	3	5	10	8
Diameter largest, cm	> 5	< 5	> 5	> 5	> 5
Time	Sync	Sync	Sync	Sync	Sync
Fong score[12]	4	3	3	4	4
Liver graft type	Deceased	Deceased	Deceased	Deceased	Deceased
ECD Type	75-yr-old donor	ABOi	> 40% steatosis	ABOi	ABOi

Abbreviations: ABOi, ABO incompatible; Bev, bevacizumab; CEA, carcinoembryonic antigen; Cetux, cetuximab; ECD, expanded criteria donor (ie, a deceased donor graft that increases the risk of early graft failure, or inferior graft and recipient survival compared with an ideal graft); FOLFIRI, folinic acid, fluorouracil, and irinotecan combination regimen; FOLFOX, folinic acid, fluorouracil, and oxaliplatin combination regimen; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan combination regimen; Fong score,[12] a clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer; KRAS, Kirsten rat sarcoma viral oncogene homolog; RFA, radio-frequency ablation; Sync, synchronous lesion (liver metastases diagnosed at the same time or within 12 months of the primary colorectal tumor); SIRT, selective internal radiation therapy; TNM, the TNM Classification of Malignant Tumors standard for stages of a primary tumor

The patient who died had progressive disease on chemotherapy pretransplant and was the only patient who tested positive for the Kirsten rat sarcoma viral oncogene homolog (KRAS) mutant. Prior to transplant, this patient had undergone 2 liver resections complicated by bleeding, which made the assessment of extrahepatic disease at the time of transplant difficult. The patient subsequently developed rapid recurrence of disease and died 10 months after transplant.

Figure 1. Survival of Nonresectable Colorectal Carcinoma Orthotopic Liver Transplant



Abbreviations: DFS, disease-free survival; NRCRC, nonresectable colorectal carcinoma; OLTx, orthotopic liver transplantation; Txp, transplant

Colorectal cancer recurrence after transplant

Recurrence of CRC occurred in all patients at a median time of 6 months after transplant (range, 3-13 months). Pulmonary recurrence occurred in 3 patients, of which 2 had subsequently undergone pulmonary resections and are presently free of disease. The remaining patient is on chemotherapy. One patient developed paraaortic lymph node recurrence, as detected on routine computed tomography scan, and is presently undergoing chemotherapy.

Discussion

To the best of our knowledge, this is the only published case series of patients undergoing liver transplant for NRCRC in Africa. Despite the use of organs that would otherwise have been discarded, thus far, the outcomes we achieved align with those in the SECA studies from Norway.

It is notable that 2 of our recipients received a marginal graft (one graft was retrieved from a 75-year-old donor, and the other graft showed more than 40% macrovesicular steatosis). The remaining 3 recipients received ABOi grafts, and all 3 of these recipients were alive at the time of writing. Additionally, none of the recipients of an ABOi graft has developed antibody-mediated rejection.

In many Asian countries, ABOi living donation has been a successful alternative to DD donation in

the face of extreme DD shortages. Antithetically, countries such as the United States discourage ABOi transplants because outcomes may not be equivalent to ABO-compatible transplants, and this may also reflect a clinical practice attuned to a more readily available pool of compatible DD grafts. Moreover, the United States has the capacity to rapidly procure matching DD organs across a sharing network supported by excellent infrastructure.

In our setting, given the proviso that we only use grafts that would otherwise be discarded, ABOi DD transplant is a likely consequence for our patients with extended oncological indications for liver transplant, such as NRCRC.

In this small proof-of-concept case series, survival exceeded that of palliative chemotherapy. Going forward, we plan to adapt our program to fit the SECA-II inclusion criteria, and we will continue to carefully monitor our outcomes. Ultimately, we hope that this strategy, as well as the use of selection criteria like those used in transplant for hepatocellular carcinoma, cholangiocarcinoma, and neuroendocrine metastases, may provide long-term survival comparable to standard indications for liver transplant.

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