

Liver transplantation for bile duct cancer

Dr Christopher A Wadsworth

Background

I am a Specialist Registrar in the Liver Unit at St Mary's Hospital, Paddington and a Clinical Research Fellow at Imperial College London. My clinical and research interest is in the diagnosis and treatment of cancer of the liver and bile ducts. I have recently completed my research studies towards a PhD in this area and I am currently writing my thesis.

Cholangiocarcinoma (CC)

The bile ducts drain bile from the liver into the small bowel. Cholangiocarcinoma (CC) is a cancer of these bile ducts. It proves rapidly fatal in over 90% of cases. In most parts of the World, complete surgical resection is the only cure for CC, as chemotherapy and radiotherapy are ineffective.^[1] Curative surgery is frequently impossible, as the tumour has already spread within the liver or beyond. This means that less than 5% of patients with CC are alive after 5-years. In the UK, one of the major causes of CC is primary sclerosing cholangitis (known as PSC). PSC is a benign disease that causes chronic inflammation in the bile ducts. CC develops in about 15% of patients with PSC, often in the patient's 30's or 40's.^[1] The development of CC in PSC patients is particularly tragic, as it tends to occur at an early age, when the patient may have a young family and otherwise a life expectancy of a further 40 years. Liver transplantation (LT) is already offered to some patients with the commonest type of liver cancer, hepatocellular carcinoma (HCC). LT for HCC is now commonplace and highly successful. However, historical attempts to transplant the livers of patients with CC have achieved very poor outcomes, with patients dying rapidly from recurrent cancer. Therefore, in the UK, LT is currently contraindicated once CC is diagnosed.^[2] Although patients with PSC frequently require LT in the late stages of their disease, development of CC currently precludes this, the only effective treatment for their disease.

The Mayo Clinic

The Mayo Clinic is located in the town of Rochester, Minnesota, USA. Two brothers, William and Charles Mayo, founded it in 1919. It remains a not for profit organisation. The Mayo treats just over a million patients a year with revenues of \$8 billion last year. It has an outstanding international reputation for clinical care and research. Since the early 1990's, the Mayo Clinic has been successfully undertaking liver transplantation in some patients with cholangiocarcinoma. It has pioneered a rigorous protocol that carefully identifies the minority of patients with CC that are likely to benefit from liver transplantation. These patients then undergo a series of pre-operative treatments and further tests before being listed for liver transplantation. The Mayo has performed the most OLTs for CC and has published numerous scientific papers on their experience and outcomes.^[3-8] Although their protocol

has been adopted and adapted by a number of other US centres, no centres in the UK are currently undertaking liver transplantation for CC.

Thanks in part to a generous grant from the St John Ambulance Air Wing, I was able to arrange a two week visit to the Mayo. The aims of my visit were:

- To experience the Mayo's liver transplantation practice
- To better understand the factors that permit successful liver transplantation in CC patients
- To hear the patient's perspective of the CC transplantation protocol
- To understand the differences between their practice and ours in the UK
- To share research ideas and establish collaborations on future studies.

My visit

I arrived in Rochester in late September; Rochester has a population of about 100,000 – 50,000 of which are employed directly by the Mayo. Many others are employed in the businesses peripheral to The Mayo - such as the dozens of hotels where patients stay whilst receiving outpatient treatment. Professor Gregory Gores, the Chair of Medicine and Head of the Department of Hepatology and Gastroenterology, hosted my visit. Prof Gores leads the liver transplantation programme at the Mayo and is a former President of the American Association for the Study of Liver Disease (AASLD) and the International Liver Cancer Association (ILCA). My time was split between the various departments that are involved in the assessment and treatment of patients with CC. I also attended multidisciplinary meetings and transplant conferences, where all liver cancer and transplant cases are discussed in an open forum of specialists.

Furthermore, I had the opportunity to give two talks during my visit: "Genetic polymorphisms and risk of cholangiocarcinoma" at the Mayo GI Seminar Series and "Endobiliary radio frequency ablation for malignant bile duct strictures" at the Mayo Hepatobiliary Neoplasia Conference. I held meetings with many of the clinician scientists who are involved with CC research.

The Transplant Process for CC

The Mayo has a strict protocol for the identification and treatment of patients with CC who may be suitable for transplantation. The diagnosis of CC must be secure, using a variety of scans and sampling techniques. Scans must show that the CC is of the type growing in the large bile ducts (extrahepatic), not deep within the liver (intrahepatic). It must not be greater than 30mm in diameter. There must be no evidence of spread outside the bile ducts or liver (on a variety of scans and other tests). The tumour must be considered unresectable with standard surgical approaches. The patient must be considered physically fit for the preoperative treatment protocol and for an eventual liver transplant.

The protocol includes exhaustive preoperative assessment, including preoperative chemotherapy, external radiotherapy and intraductal brachytherapy (when radiotherapy is applied directly into the bile duct).

Patients who tolerate this gruelling pre-operative regime, and have no evidence of spread of the cancer at an exploratory operation, undergo transplantation.

In total, The Mayo performed a total of 271 adult liver transplants in the last two years with excellent outcomes, well above the US average. An increasing number of their liver transplants (including those for CC) involve live related donors. In their most recently published data, they have entered 184 CC patients into their transplantation protocol. 120 have actually undergone liver transplantation. Five-year survival after transplantation is 73%, with 18% of those undergoing transplant developing recurrent CC. The 5-year survival figures are comparable to those achieved with LT for other diseases. None of these patients would have received a LT in the UK and all would almost certainly have died. The excellent survival figures are likely the result of the meticulous selection of cases and the exhaustive pre-operative protocol.

The patients:

The resources available mean that patients receive top class care. The buildings are modern and spacious, with lots of natural light. The clinical environments are clean and smartly decorated. All inpatients have private rooms, enhancing privacy and dignity. Appointments with specialists were unhurried, as clinics are not overbooked. It is clear that patient safety is paramount, with patient satisfaction a close second. I met a numerous patients who were at different stages of the transplant process. One young man with PSC related CC was half way through the pre-transplant chemotherapy and radiotherapy. In most parts of the world this man would not have a curative treatment available. Fortunately he was considered to be a candidate for transplantation and was optimistic about his future, even in the midst of the side effects of chemoradiotherapy. A patient who had received a transplant for CC over ten years ago was attending for routine follow up. After such an interval, she can be considered cured of CC, although she must continue to visit the clinic for the management of her post transplant immunosuppression. I also met one patient who, sadly, had suffered a recurrence of his CC three years after transplantation. Such recurrences occur in a small minority of patients but, even with very careful selection and treatment, not all patients who receive a transplant for CC will be cured. The patients that I met during my visit voiced unanimous pride and faith in the Mayo. The efficiency with which the institution can operate and the time and environment that patients are offered are clearly important factors in the Mayo's enduring success.

Conclusion

The visit has enhanced my professional development and my understanding of the strategy they use to achieve great outcomes. It has allowed me to develop ongoing collaborative research links with some of the clinician scientists there. I will be presenting much of what I experienced and learnt at the Mayo within my own institution and at regional meetings in the UK. I have better understood the technical, clinical, systematic and financial factors required to provide liver transplantation to some CC patients.

I personally hope that we will eventually be able to offer CC patients in the UK liver transplantation. Whether, and when, this might be possible is not clear. There is huge demand for donor organs in the UK and, with such a shortage of donors, it is difficult to offer transplantation to new patient groups. Almost all publications on successful transplantation in CC have emanated from the Mayo. It is therefore difficult to draw conclusions about the reproducibility of their outcomes in other centres. However, several other US centres have now adopted their protocol. If these independent centres are able to show comparable success, this will strengthen the case in other countries around the world. Finally, the financial cost of the Mayo protocol may pose a further hurdle in publically funded healthcare systems.

Obtaining the support of the St John's Ambulance Air Wing Travelling Fellowship has permitted me a great learning experience. The service offered at the Mayo Clinic is unique, so it would not have been possible to gain this experience at any UK or European centre. My experiences will allow me to enhance the management of my own patients, and my contribution to the development of our wider service.

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