INTRODUCTION

The burgeoning numbers of patients who undergo cardiac or pulmonary transplantation make it increasingly important that cardiologists, pulmonologists and cardiothoracic surgeons be familiar with the complications of these treatments. One of these is an increased risk for the development of certain types of cancer. Much of this chapter is based on experience obtained from renal transplantation, but whenever possible observations made in cardiac, cardiopulmonary or pulmonary graft recipients (henceforth referred to as cardiothoracic [CT] recipients) will be stressed. The report is based on data collected by the Cincinnati Transplant Tumor Registry (CTTR) up till May 1995.

The chapter will consider three categories of malignancies: (a) transplanted cancers; (b) pre-existing tumors that were present before transplantation; and (c) de novo malignancies that developed in the recipient after transplantation.

TRANSPLANTED MALIGNANCIES

When assessing a potential cadaver donor for harvesting the heart or lungs, it is obligatory to determine whether or not he or she has cancer, or has been treated for it recently, as there is a danger of transmitting tumor cells with the transplanted organ(s). Normal individuals such foreign cells would be rejected promptly by the recipient. However, the immunosuppressive therapy, used to prevent graft rejection, impairs the host's immune defenses and prevents destruction of cancer cells which may grow, invade adjacent structures, and even metastasize.

The CTTR has data on 248 recipients of organs from donors who had malignancies at the time of donation, or had been treated for them within 10 years of transplantation or, in the case of the several living donors, who presented with neoplasms up to 18 months after donation. Allograft recipients included 227 renal, 10 hepatic, seven cardiac, two pancreatic, one cardiopulmonary and one pulmonary. In eight instances small tumors were removed from renal allografts immediately prior to transplantation. If we include these cases 103 recipients (42%) received organs that contained cancers. In 39 instances the tumor involved the allograft only, while in another six there was invasion of adjacent structures, and 58 recipients had distant metastases.

The most common tumors that caused metastases were malignant melanoma (28%), carcinoma of the kidney (19%), carcinoma of the bronchus (17%), choriocarcinoma (16%) and primary brain tumors (9%). Overall, 40 recipients died of cancer. However, 16 renal allograft patients had complete remissions of all transmitted neoplasms, usually following allograft nephrectomy, and cessation of immunosuppressive therapy, which presumably permitted host immunity to recover and reject residual tumor. These measures were supplemented in five patients by chemotherapy, immunotherapy (interferon; interleukin-2) or radiotherapy. Two other patients are currently alive with tumor after undergoing allograft nephrectomy and discontinuation of immunosuppressive therapy.

Seven heart, one heart-lung and one lung patients received organs from donors with cancer. Four recipients (three heart, one lung) died of metastases of carcinoma of the bronchus, medulloblastoma, malignant melanoma, and nephroblastoma respectively. The heart-lung recipient died of rejection 1 month after transplantation. At autopsy a metastasis of choriocarcinoma was found in one lung. Four cardiac recipients are alive from 0.5 to 57 (average 29) months after transplantation without evidence of malignancy, having received organs from donors with choriocarcinoma, adenocarcinoma of the uterine cervix, adenocarcinoma of the kidney, and carcinoma of the prostate, respectively.

While it is possible to remove part or all of a lung allograft that contains a metastasis, excision of a cardiac allograft and cessation of immunosuppressive therapy are not feasible unless an implantable artificial heart can be used, either as a permanent replacement or for a period of several months until all evidence of malignancy has disappeared and a new cardiac allograft can be inserted. None of these procedures has yet been attempted to treat transmitted malignancies in CT recipients.

It is therefore imperative to avoid using donors with tumors, except those with low-grade carcinomas of the skin, or with primary brain malignancies, which rarely spread outside the central nervous system. However, it is important to have histologic proof that the cancers actually arose in the brain, as in
several instances, the cause of the donor's death was misdiag-
nosed as intracranial hemorrhage, primary brain tumor, or multi-
ple brain abscesses. When, in fact, the donors died of metastases
mostly from choriocarcinoma, bronchial carcinoma, malignant
melanoma, or renal carcinoma. We should also avoid using
donors with primary brain tumors who have been treated with
ventriculoperitoneal or ventriculovenous shunts, or who have had
extensive craniotomies, radiotherapy or chemotherapy, as these
open pathways for tumor dissemination.

PRE-EXISTING CANCERS

If a neoplasm in the potential recipient was treated before trans-
plantation, it is possible that the immunosuppressive therapy may
impair the ability of the host's immune defenses to control any
residual cancer cells.

In a study of 939 pre-existing malignancies that occurred in
913 renal transplant recipients there was a 22% recurrence rate
after transplantation. Thirteen percent of the recurrences oc-
curred despite removal of the primary malignancies 5 or more
years beforehand. It was recommended that with the exception of
patients with: (a) incidentally discovered renal malignancies, (b)
in situ carcinomas of various organs, (c) focal neoplasms (a small
microscopic focus) in organs such as the prostate or uterus, (d)
low-grade bladder cancers and (e) basal cell carcinomas of the
skin, transplantation should be delayed for at least 24 months
after treatment of the tumors.

During this time renal transplant patients can be kept alive by
dialysis. As regards potential cardiac transplant recipients, current
experience with the artificial heart makes it extremely unlikely
that they can be kept alive during this long waiting period.
Because of the hopeless prognosis of potential heart recipients
who do not receive transplantation, it is probably advisable to expedi-
tiously proceed with transplantation as soon as donor organs
become available, except in individuals with active major cancers
or who have short life expectancies because of their neoplasms.

Pre-existing tumors (total 160) were present in 146 heart, eight
lung and two combined heart-lung recipients who were treated
from 504 months before to 12 months after transplantation
(average 86 months before transplantation). Persistence or recur-
rence of cancer occurred in 30 patients (19%), a similar percent-
age to that observed in renal transplant recipients.

A favorable feature in many heart transplant recipients is that
they had been successfully treated for a lymphoma (including
Hodgkin's disease) or a sarcoma more than 5 years previously,
and were apparently cured of their malignancies. Adriamycin-
induced cardiotoxicity was a common indication for cardiac
transplantation in these patients.

Of the 30 patients with persistent or recurrent tumors, 12 had
tumors treated at or after transplantation, five were treated 24
months or less before transplantation, nine were treated more than
24 months before transplantation, and the time of treatment was
not stated in four cases. The most common tumors that persisted
or recurred were carcinomas of the lung (seven), non-melanoma
skin cancers (five), lymphomas (four), carcinomas of the bladder
(three) and carcinomas of the pancreas (two). In addition, two pa-
tients had primary tumors of the heart (malignant synovioma and
angiosarcoma, respectively) removed at the time of transplanta-
tion and both, not surprisingly, had recurrences.

DE NOVO TUMORS

The CTTR has data on 8191 patients who developed 8724
cancers de novo after transplantation. Of these, 772 received
heart, and 29 combined heart-lung, and 29 lung allografts. There
were also 6821 kidney transplant recipients and 540 recipients of
other extrarenal organs (liver, pancreas, bone marrow, upper
abdominal cluster organs and small bowel).

Data from several large renal transplant centers show an overall
incidence of cancer ranging from 1% to 16%, with an average of
6% . In a series of 182 cardiac transplant recipients who under-
went 199 transplantations, the incidence was 10% . Lanza et al.
compared the incidence of malignancies in cardiac and renal allo-
graft recipients. They found a 2-fold greater increase of all neo-
plasms in cardiac patients, with nearly a 6-fold increased
incidence of visceral tumors (p < 0.02). They attributed the in-
crease to the more intense immunosuppressive therapy used in
these patients.

The incidence of cancer increases with the length of follow-up
after transplantation. The actuarial probability of developing ma-
lignancy among patients who received cardiac transplants during
childhood was 7% at 1 and 2 years, 12% at 3 years, and 15% at 4
and 5 years . An Australasian study of 6596 recipients of cadaver
renal transplants showed that the percentage probability of devel-
opng cancer 24 years after transplantation was 66% for skin neo-
plasms, 27% for non-skin malignancies and 72% for any type of
tumor. These exceptional figures must be interpreted with
cautions as most malignancies were skin cancers (which are very
common in Australia) and the number of 24-year survivors was
small. Nevertheless, they stress the necessity to follow transplant
patients indefinitely.

Age of recipients

The malignancies affected a relatively young group of persons
whose average age at the time of transplantation was 42 years
(range 3 months to 80 years). Forty-three percent were under 40
years of age at the time of transplantation.

Sex

Males made up two-thirds and females one-third of the patients
with cancer, roughly the same proportions as those undergoing
renal transplantation.

Time of appearance of the neoplasms

In the general population there is a latent period of 5-20 years or
even more, between exposure to many carcinogens and the de-
velopment of malignancies. However, in transplant patients tumors
appeared after a much shorter interval, at an average of 61,
median 46 (range 0.25-313) months.

Some cancers appeared at fairly distinct intervals after trans-
plantation. Kaposi's sarcoma (KS) presented the earliest at an
average of 75, median 60 (range 1-313) months post-