Utility of Long-term Surveillance Endomyocardial Biopsy: A Multi-institutional Analysis

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Background: The utility of long-term endomyocardial biopsy surveillance in heart transplant recipients has been questioned. This study was undertaken to identify risk factors for late rejection and to examine the impact of different biopsy surveillance protocols on outcomes using the registry of the Cardiac Transplant Research Database.

Methods: The study group consisted of all adult patients who underwent heart transplantation at the 33 centers participating in this investigation between January 1, 1993 and January 1, 2002, survived past the second post-transplant year, and were followed-up by a defined surveillance biopsy protocol.

Results: During a follow-up that consisted of 24,137 patient-years, 1,626 late rejections occurred. Shorter time since transplant, history of rejection, younger age and African-American ethnicity of the recipient were strong risk factors for late rejection. The practice of surveillance biopsy varied among institutions. Continued surveillance increased the rate of diagnosis of late rejection (RR = 1.3, p = 0.002). There was no reduction in the incidence of hemodynamically compromising rejection and no increase in survival in patients with long-term vs intermediate-term surveillance. Short-term surveillance was associated with an increased incidence of hemodynamically compromising rejection, particularly among high-risk patients, and increased mortality in African-American patients.

Conclusions: There are no apparent benefits from surveillance biopsy beyond 5 years post-transplant. Surveillance biopsy between 2 and 5 years post-transplant was found to reduce mortality in African-American recipients. Non–African-American recipients at high risk for late rejection will likely benefit from surveillance up to 5 years post-transplant. J Heart Lung Transplant 2006;25: 1402–9. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Endomyocardial biopsy is the test of choice for diagnosing acute graft rejection in cardiac transplant recipients. The three general indications for endomyocardial biopsy are: (1) clinical suspicion of acute rejection, such as constitutional symptoms, evidence of graft dysfunction or hemodynamic compromise; (2) assessment of response to change in immunosuppressive therapy; and (3) surveillance to detect clinically silent rejection in patients on a stable immunosuppressive regimen. The majority of endomyocardial biopsies are performed for the purpose of routine surveillance. The rationale for surveillance biopsies lies in the potential for prevention of progression to a more severe form of rejection by timely anti-rejection therapy. Acute rejection has also been linked to coronary artery vasculopathy,[1–4] and treatment of clinically silent rejection might decrease progression of this disease. On the other hand, overtreatment of clinically silent rejection may increase the risk of infection and malignancy and cause other side effects associated with augmented immunosuppressive therapy.[5] Furthermore, biopsies are accompanied by procedural risks, patient discomfort and increased expense.

These considerations raise the question of whether the benefits of long-term surveillance biopsies outweigh the potential disadvantages. This question is particularly important for patients in whom the likelihood of rejection is low. The frequency of acute graft rejection is highest in the first few months after transplantation, but decreases significantly by the end of the first year.[6]

The incidence and predictors of late rejection in adult and pediatric heart transplant recipients have been examined in several studies.[7–13] The results have not

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been uniform, and there is no consensus on benefits and cost-effectiveness of long-term surveillance endomyocardial biopsy in all patients.[8–10,14–17]

This study was designed to examine the utility of long-term biopsy surveillance using a large multi-institutional database.

METHODS

Data Collection

Patient-specific data were abstracted from the Cardiac Transplant Research Database (CTRD), a registry of cardiac transplant clinical data collected through event forms from participating institutions. All centers obtained institutional review board approval for participation in the CTRD.

Center-specific information regarding frequency and duration of surveillance biopsies, timing of repeat biopsies after episodes of rejection, and exceptions and recent changes to surveillance protocols were obtained through e-mail questionnaires. Responses were obtained from 33 centers. The study centers are listed in the Appendix.

Patient Population

The study group consisted of all adult patients who underwent heart transplantation at the 33 centers participating in this study between January 1, 1993 and January 1, 2002, survived past the second post-transplant year, and were followed by a defined surveillance biopsy protocol. There were 4,932 such patients. Age at transplantation was 52 ± 10.8 years, and 3,873 patients (79%) were male. The ethnic background was white in 86%, African-American in 11% and other in 3%.

Definitions

Late rejection was defined as an event occurring after the end of the second post-transplant year that was treated with temporary augmentation of immunosuppression and was considered clinical rejection by the transplant team. Most commonly (67%), the rejection episode was associated with an endomyocardial biopsy of ISHLT Grade 2R or higher. Severe hemodynamically compromising (HC) rejection was defined as clinical rejection associated with depressed left ventricular ejection fraction (≤0.45) immediately before or during the episode of treated rejection and the need for inotropic support.

Surveillance Biopsy Protocols

Institutional practice of routine biopsy surveillance varied widely. The cessation of protocol biopsy surveillance ranged from very early termination (in the first post-transplant year) to indefinite surveillance (Figure 1). Institutions were divided into three groups based on whether their practice was: (1) to discontinue surveillance biopsy <5 years post-transplant (short-term surveillance group); (2) to discontinue surveillance biopsy at 5 years post-transplant (intermediate-term surveillance group); or (3) to continue surveillance biopsy for ≥10 years (long-term surveillance group).

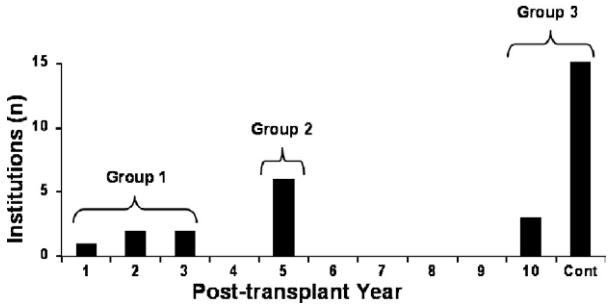

Figure 1. Institutional practice of biopsy surveillance. Differences in duration of biopsy surveillance among the institutions participating in this study from the Cardiac Transplant Research Database. Group 1: surveillance <5 years (5 centers, $n = 522$); Group 2: surveillance ending at 5 years (5 centers, $n = 1{,}162$); Group 3: surveillance ≥10 years (18 centers ($n = 3{,}073$). Note: 175 patients were followed with other protocols.

Data Analysis

Risk factors for late rejection were identified using modulated renewal parametric regression analysis in the hazard function domain. This method has been described in detail by Blackstone et al.[18] A free copy of the statistical software that allows use of this method for hazard function analysis can be downloaded from www.clevelandclinic.org/heartcenter/hazard. Events of interest and relevant variables in this analysis were studied in 12-month intervals, starting at 2 years after transplant, resetting Time 0 at each anniversary. When exploring the effect of continued surveillance on rejection risk, the events were stratified into a continued-surveillance or a no surveillance group, based on the protocols provided by participating institutions. For each 12-month period, the patient data were entered into the appropriate group according to the specific institutional surveillance protocol.

Clinical outcomes, specifically rejection with hemodynamic compromise and survival, were examined using parametric regression analysis in the hazard function domain starting at Year 2. Kaplan–Meier curves were constructed to depict freedom from an event. Risk factors for late rejection were explored by multivariate analysis in the hazard function domain.

RESULTS

Incidence of Late Rejection

During the period of study, 1,472 rejection episodes were identified at >2 years post-transplant. Figure 2

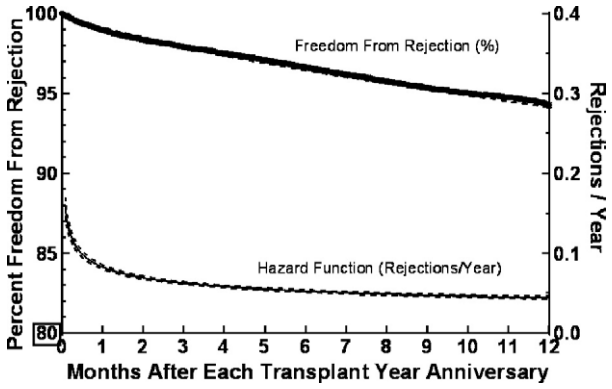

Figure 2. Parametric survival curve depicting freedom from rejection in a 12-month interval after transplant year anniversary (solid line). Hazard function describes the risk of rejection over time in a 12-month interval after transplant year anniversary. The dashed lines indicate the 70% confidence limits.

depicts the freedom from late rejection after each transplant anniversary. The likelihood of rejection over the ensuing 12 months was about 5%.

In 67% of the patients treated for rejection, there was evidence of moderate (ISHLT Grade 2R) or severe (ISHLT Grade 3R) cellular rejection on endomyocardial biopsy. Among patients with hemodynamic compromise, 50% had evidence of at least moderate cellular rejection on endomyocardial biopsy. Antibody-mediated rejection—a diagnosis for which there was no consensus during much of the time period in which our data were obtained—may therefore have a significant role even late after transplant. With the recent inclusion of antibody-mediated rejection in the ISHLT classification, future studies may be able to characterize this role more directly.

Table 1. Multivariate Analysis of Rejection After Second Anniversary of Transplant (Modulated Renewal at Each Anniversary Post-transplant)

Variable value during anniversary year	*p*-value	Relative risk
Time since transplant	<0.0001	2.4 (Year 2 vs 5)
Greater recipient body mass index at transplant	0.03	1.2 (35 vs 20)
History of post-Tx infection	0.006	1.3[a]
Shorter time since last infection	0.04	1.3
Continued surveillance		
Younger age at transplant	<0.0001	1.4 (35 vs 60)
African-American recipient	<0.0001	1.4
History of rejection	<0.0001	1.5[b]
Shorter time since last rejection	<0.0001	1.5
Greater number of previous rejections	<0.0001	1.5
Discontinuation of surveillance		
Younger age at transplant	0.0005	2.6 (35 vs 60)
African-American recipient	0.05	2.1
History of rejection	0.002	2.5[b]
Shorter time since last rejection	0.01	2.5
Greater number of previous rejections	0.02	2.5

[a]No infection history vs infection 6 months earlier.
[b]No rejection history vs 2 rejections with the last rejection 1 year earlier.

Risk Factors for Late Rejection

Variables identified as risk factors for late rejection are depicted in Table 1. Shorter time since transplant and shorter time since last rejection, as well as the number of previous rejections, younger age of the recipient, and African-American ethnicity of the recipient, were strong risk factors for late rejection. Recent infection episode and higher body mass index of the recipient were additional modest predictors of late rejection.

To determine whether continued biopsy surveillance affected the rate of detection of late rejection, we added "surveillance biopsy" as a variable in the model. The effect of the presence or absence of continuation or discontinuation of surveillance biopsies was significant as an interaction term with other risk factors related to recipient age, race and prior rejection. The relative risk values for these interactions are shown in Table 1.

Surveillance in Different Risk Groups

To better understand the interactions between surveillance and risk of late rejection we examined the predicted probability of rejection in the ensuing 12 months as a function of continued surveillance in patients with differing risks for late rejection. Figures 3 to 5 are nomograms of solutions to the multivariate analysis shown in Table 1. Figure 3 shows the predicted probability of rejection in a low-risk patient. The risk of late rejection was relatively small in both the surveillance and no-surveillance groups, and the probability of

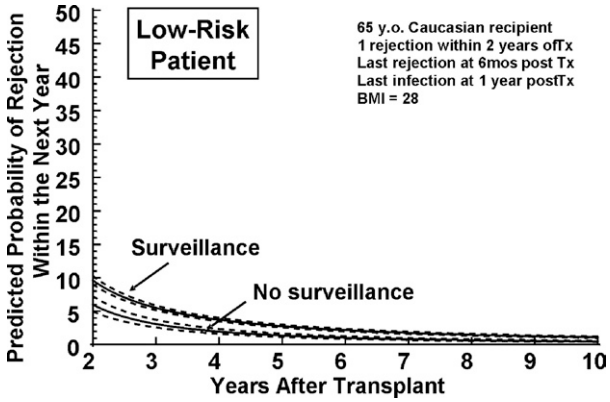

Figure 3. The solution of the multivariate equation for rejection after the second post-transplant year, depicting probability of late rejection in a low-risk patient under continued biopsy surveillance (upper curve) and no biopsy surveillance (lower curve). The dashed lines represent the 70% confidence intervals. The values of specific variables in the equation for this depiction are displayed.

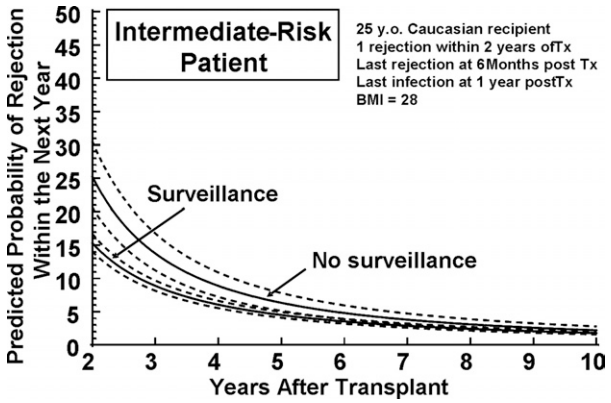

Figure 4. Solution of the multivariate equation (see Table 1) for an intermediate-risk patient under continued biopsy surveillance (lower curve) and no biopsy surveillance (upper curve). Dashed lines represent 70% confidence intervals. The values of specific variables are indicated.

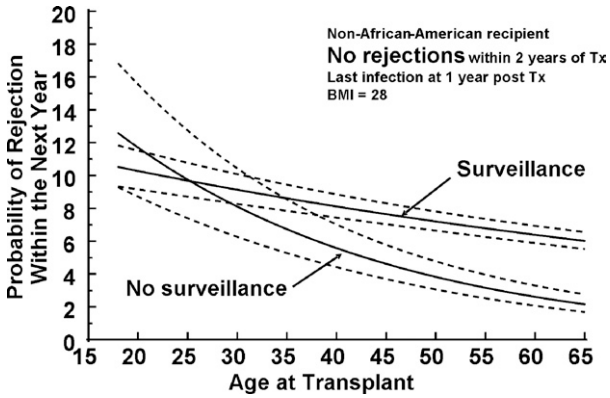

Figure 6. Solution of the multivariate equation for rejection within 1 year in relation to age at transplant, stratified by presence or absence of surveillance biopsies, for non–African-American recipients. Values of other variables are shown.

detecting rejection was slightly higher in the surveillance group. For an intermediate-risk patient (Figure 4), the risk of late rejection was slightly higher in the no-surveillance group for the first 4 years post-transplant, after which there was no difference. Finally, in a high-risk patient, the risk of rejection was considerably higher in the no-surveillance group out to about 7 years post-transplant (Figure 5). The impact of race or rejection surveillance is shown in Figures 6 and 7. In the absence of rejection during the first 2 years, non–African-American recipients younger than approximately 40 years of age had a similar incidence of late rejection regardless of the biopsy protocol. At >40 years of age, surveillance biopsies increased the likelihood of detecting rejection (Figure 6). Among African-Americans (Figure 7), the discontinuation of a surveillance biopsy increased the risk of clinical rejection in patients younger than about 40 years of age.

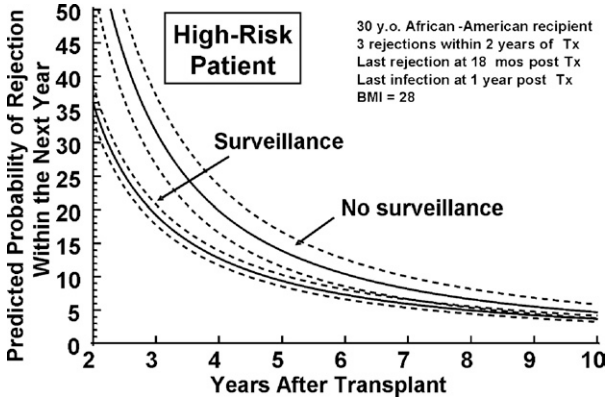

Figure 5. Similar depiction to that shown in Figures 3 and 4, except this depiction is solved for a higher risk recipient.

Influence of Institutional Surveillance Protocols on Rejection With Hemodynamic Compromise

The aforementioned findings suggested that a surveillance biopsy protocol reduces the incidence of clinically manifest rejection in high-risk patients. To examine the possibility that surveillance biopsy protocol influences long-term outcomes, we examined clinical outcomes as a function of surveillance biopsy practice at the participating centers (see Methods).

Predictors of severe hemodynamically compromising (HC) rejection are shown in Table 2. Discontinuation of surveillance biopsies <5 years after transplant (short-term surveillance) led to a 2.4-fold increase in the risk of severe HC rejection. The rest of the predictors of severe HC rejection were similar to those identified as predictors of any late rejection. The negative impact of discontinuation of surveillance biopsies <5 years post-transplant on the risk of severe HC rejection was most pronounced in African-American recipients (Figures 8 and 9).

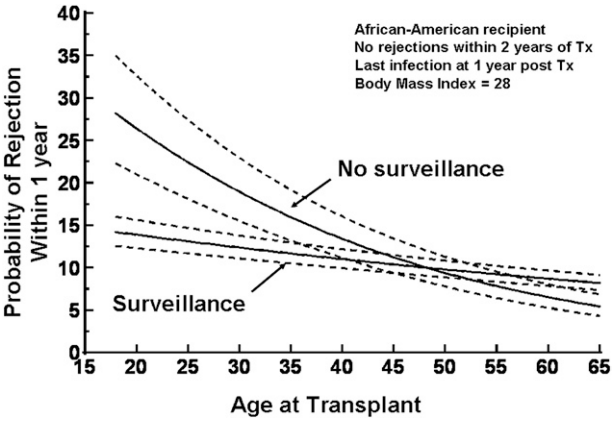

Figure 7. Solution of the multivariate equation for rejection within 1 year in relation to age at transplant, stratified by presence or absence of surveillance biopsies, for African-American recipients.

Table 2. Multivariate Analysis of Severe HC Rejection After Second Anniversary of Transplant

Variable value at 2-year anniversary of Tx	*p*-value	Relative risk
Previous severe HC rejection	<0.0001	5.0
Previous HC rejection not requiring inotropic support	0.005	1.8
Younger age of recipient	<0.0001	2.0 (35 vs 55)
Larger body mass index of recipient	0.003	1.8 (30 vs 20)
Earlier date of transplant	<0.0001	2.0 (5 years)
African-American recipient	<0.0001	3.0
Protocol stopping surveillance <5 years post-Tx	0.0001	2.4

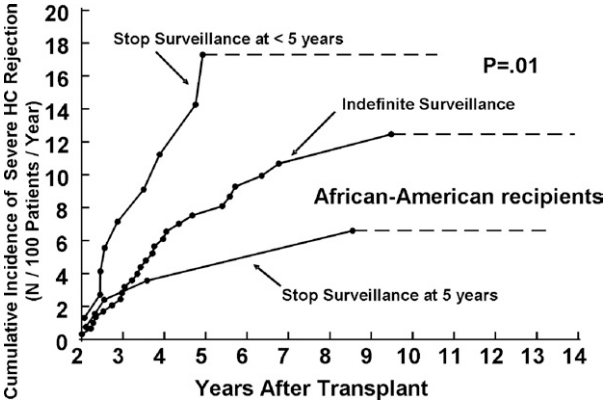

Figure 9. Cumulative incidence of severe hemodynamically compromising rejection in African-American recipients followed by short-, intermediate- and long-term biopsy surveillance protocols.

Influence of Institutional Protocol on Survival

The causes of death after the second post-transplant year are listed in Table 3. By multivariate analysis, identified risk factors for mortality are listed in Table 4. Among non–African-American recipients, there was no difference in survival when stratified by surveillance biopsy protocol (Figure 10). However, a protocol of surveillance biopsy discontinuation before 5 years post-transplant in African-Americans after the second transplant anniversary resulted in lower late survival (Figure 11).

Institutional Surveillance Protocol and Immunosuppressive Therapy

Direct comparison of intensity of immunosuppressive therapy among the different groups was difficult because of the variety of immunosuppressive regimens used by the centers as well as changes in immunosuppressive therapies in time. We therefore focused our analysis on the use of steroids as part of the immunosuppressive regimen. Although there were differences in the approach to steroid tapering among the individual centers, there was no clear correlation between the duration of surveillance protocol and proportion of patients on prednisone. In addition, among patients taking prednisone, the prednisone dose (milligrams per kilogram per day) was nearly identical at different time-points after transplant among patients in the three surveillance strategy groups.

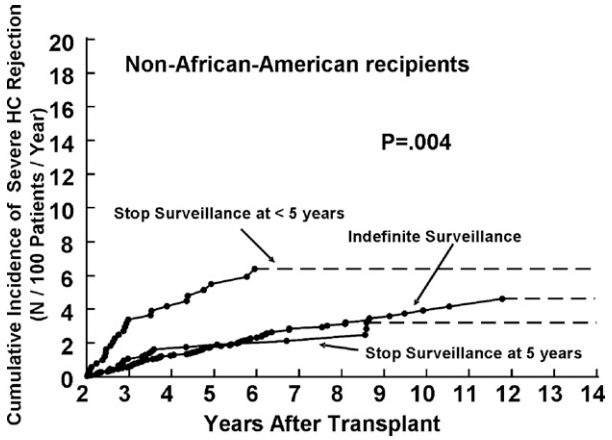

Figure 8. Cumulative incidence of severe hemodynamically compromising rejection in non–African-American recipients followed by short-, intermediate- and long-term biopsy surveillance protocols (see text for definitions).

Table 3. Primary Causes of Death After 2 Years Post-Tx

Cause of death	During surveillance		After end of surveillance	
CAD, infarction	138	19%	46	19%
Malignancy, non-lymphoma	126	18%	51	21%
Lymphoma	39	5%	9	4%
Other (specify)	71	10%	32	13%
Sudden cardiac death	64	9%	28	11%
Rejection	45	6%	7	3%
Neurologic	30	4%	7	3%
Non-specific graft failure	31	4%	9	4%
Multi-system failure	17	2%	11	4%
Renal failure	15	2%	5	2%
Respiratory failure	13	2%	4	2%
Hepatic failure	7	1%	1	—
Pulmonary embolism	7	1%	1	0.4%
Accidental	6	0.8%	—	—
Cardiac failure	4	0.6%	2	0.8%
Arrhythmic	2	0.3%	—	—
Aspiration pneumonia	2	0.3%	1	0.4%
Hemorrhage	2	0.3%	1	0.4%
Pulmonary hemorrhage	—		1	0.4%
Suicide	2	0.3%	1	0.4%
Total of known causes of death	712	100%	248	100%
Unknown	87	11%	24	9%
Total	799	100%	272	100%

Table 4. Multivariate Analysis of Death After Second Anniversary of Transplant

Variable value at 2-year anniversary of Tx	*p*-value	Relative risk
Greater number of previous rejections	0.08	1.3 (3 vs 0)
Post-Tx rejection	0.02	2.0
Days since last rejection	0.02	1.3 (30 days vs 1 year)
Number of post-Tx HC rejections	0.01	1.4 (1 vs 0)
Greater number of previous infections	0.001	1.3 (2 vs 0)
Post-Tx infection	0.008	2.4
Days since last infection	0.005	1.4 (30 days vs 1 year)
No angiogram done in first 2 years post-Tx	<0.0001	1.5
Mild CAD on last angiogram	<0.0001	1.6
Moderate CAD on last angiogram	<0.0001	2.1
Severe CAD on last angiogram	<0.0001	2.5
Post-Tx malignancy (not lymphoma or skin cancer)	<0.0001	2.7
Post-Tx lymphoma (number of occurrences)	0.02	2.0 (1 vs 0)
Earlier date of transplant	<0.0001	1.7 (5 years)
LVEF on last echocardiogram (lower)	0.04	1.7 (25 vs 55)
Pre-Tx history of peripheral vascular disease	0.0005	1.6
Younger recipient age	0.002	1.7 (25 vs 45)
Older recipient age	0.003	1.7 (65 vs 45)
African-American recipient	0.08	1.2
If African-American and stopping surveillance <5 years post-Tx	0.001	2.3
Pre-Tx history of smoking (still smoking within 6 mos of listing)	0.001	1.4
Pre-Tx history of smoking (stopped >6 months from listing)	0.02	1.2
Pre-Tx history of diabetes	<0.0001	1.5
Older donor age	0.04	1.1 (40 vs 20)
Protocol stopping surveillance <5 years post-Tx	0.13	1.2

DISCUSSION

Summary of Findings

With the current immunosuppressive regimens, the risk of acute rejection late after cardiac transplantation is low. For this reason, the benefits of long-term surveillance endomyocardial biopsies in cardiac transplant recipients have been questioned. However, consensus is lacking regarding the advisable time period for routine surveillance biopsies after cardiac transplantation. Using multi-institutional data, we have identified risk factors for late rejection, including recipient age at transplant, recipient ethnic origin and recipient rejection and infection history, and we have examined the effects of different surveillance biopsy approaches on clinical outcomes in transplant recipients at different levels of risk. To our knowledge, our work represents the first multi-institutional study to address the question of the utility of long-term biopsy surveillance.

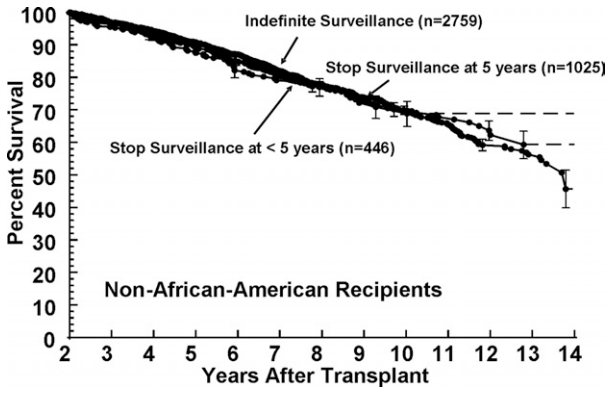

Figure 10. Actuarial survival for non–African-American recipients followed by short-, intermediate- and long-term biopsy surveillance protocols. Vertical bars represent 70% confidence intervals.

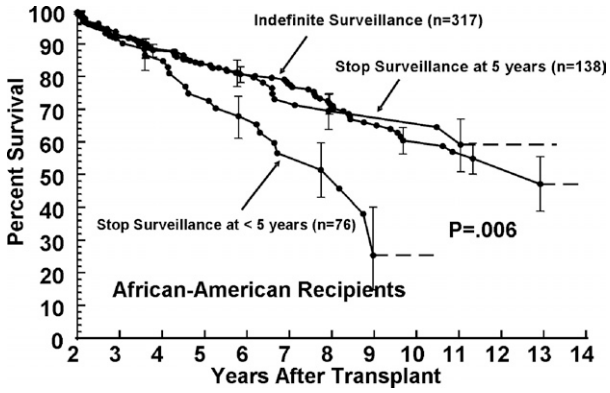

Figure 11. Actuarial survival for African-American recipients followed by short-, intermediate- and long-term biopsy surveillance protocols.

Regarding protocols for duration of surveillance biopsies, we did not find any benefit with respect to the incidence of hemodynamically compromising rejection or survival comparing long-term (≥10 years) with intermediate-term (5 years) surveillance. At the same time, we found no evidence of a deleterious effect of long-term biopsy surveillance. In contrast, intermediate-term surveillance biopsy resulted in a lower risk of hemodynamically compromising rejection than did short-term (<5 years) surveillance, and this was accompanied by a survival advantage in African-American patients, which may reflect their increased risk of rejection.[19–21]

There are several possible explanations for this phenomenon. African-American patients are more likely to receive donor organs with more HLA mismatches than white patients.[22] In addition, different polymorphism frequencies between African-Americans and non–African-Americans with respect to genes that participate in regulation of immune response have been linked to the increased incidence of rejection in African-Americans.[23] Racial disparities in access to medical care have been proposed as a factor influencing outcomes in several aspects of cardiac disease.

Effect of Surveillance Biopsies

The rationale for surveillance biopsy rests upon the premise that improved detection of rejection in its earlier stages will lead to changes in immunosuppressive therapy, reduce progression to more severe rejection, and improve survival. Although our results showing advantages of intermediate-term surveillance in certain patient sub-groups are consistent with this assumption, other explanations for the benefits of intermediate-term surveillance cannot be excluded. Because death as a direct result of late rejection is relatively uncommon, it may be that differences in the frequency of interactions between patients and their transplant care providers, rather than differences in surveillance frequency per se, conferred the survival advantage in African-American recipients. More frequent interactions might have resulted in increased medication compliance, more frequent laboratory monitoring of immunosuppressive drug levels, or more frequent use of other diagnostic tests. The nature of the data contained in the database does not allow us to determine whether this was the case.

Recommendations Regarding Surveillance Biopsies

This study provides support for the safety of discontinuation of routine biopsy surveillance at 5 years post-transplant. The results also support a policy of continuing biopsy surveillance for at least 5 years post-transplant in African-American recipients, in whom the risk of both hemodynamically compromising rejection and mortality is higher when surveillance is stopped earlier. For non–African-Americans, specific recommendations are more problematic. Although we observed no mortality benefit with intermediate-term vs short-term surveillance, we did observe a statistically significant benefit with respect to hemodynamically compromising rejection. On the other hand, our data suggest that this benefit might amount to a reduction of only 3 episodes of hemodynamically compromising rejection per 100 patients between Years 2 and 5. When one considers that patients may undergo at least 6 biopsies over this 3-year period, it would appear that at least 200 biopsies would be required for each episode of hemodynamically compromising rejection to be prevented, without clear survival benefit. When one considers the financial costs, discomfort and potential risks of endomyocardial biopsies, the value of intermediate-term surveillance biopsy in non–African-American patients without other major risk factors and without recent rejection must be questioned.

Study Limitations

There are important limitations to our findings, which are inherent in work with registry data. Identification of rejection depends on frequency of surveillance biopsies, temporal proximity of repeat biopsy to the one by which rejection was diagnosed, as well as the interpretation of the histologic findings by individual pathologists. As these were not standardized among the different centers, some variability is unavoidable. Immunosuppression protocols, including steroid-weaning and rejection-treatment protocols, were likewise not standardized among the centers. Although we hypothesize that surveillance biopsy is likely to result in increased detection of mild forms of cellular rejection in high-risk patients, and that therapy started as a result will prevent the development of high-grade cellular rejection, this cannot be directly inferred from the present data.

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APPENDIX

CTRD Centers Participating in Surveillance Biopsy Study

ANH	Abbott Northwestern Hospital/Minneapolis Heart Institute
BWH	Brigham and Women's Hospital
CCF	Cleveland Clinic Foundation
DHT	Downstate Heart Transplant Center, Peoria
GNV	University of Florida, Shands Hospital
HFH	Henry Ford Hospital
HMC	Hershey Medical Center, Penn State University
HUP	University of Pennsylvania
IUI	Indiana University Medical Center
JHH	Johns Hopkins Hospital
LUM	Loyola University Medical Center
MAH	Mid-America Heart Institute of St. Luke's Hospital
MCV	Medical College of Virginia
MGH	Massachusetts General Hospital
MHI	Methodist Hospital of Indianapolis
MMC	Mayo Clinic - St. Mary's Hospital
OSU	Ohio State University
RPC	Rush-Presbyterian - St. Luke's Med Center
SCC	Medical University of South Carolina
SHP	Sharp Memorial Hospital
SLH	St. Luke's Episcopal Hospital, Houston
TMH	Baylor College of Medicine/The Methodist Hospital
TUH	Temple University Hospital
UAB	University of Alabama at Birmingham
UCM	University of Cincinnati Medical Center
UIO	University of Iowa Hospitals & Clinics
UMN	University of Minnesota
UTA	Utah Transplant Affiliated Hospitals
UTS	University of Texas Southwestern/St. Paul Med Center/Baylor
WUM	Washington University Medical Center