Digestive Diseases and Sciences, Vol. 43, No. 9 (September 1998), pp. 1931–1937

# Role of Splenectomy in Human Liver Transplantation Under Modern-Day Immunosuppression

FAROKH SAMIMI, MD, WILLIAM D. IRISH, MSc, BIJAN EGHTESAD, MD, ANTHONY J. DEMETRIS, MD, THOMAS E. STARZL, MD, PhD, and JOHN J. FUNG, MD, PhD

Between January 1987 and October 1991, 1466 patients underwent consecutive Orthotopic Liver Transplantation (OLTx) at the University of Pittsburgh. Forty of these patient's had concomitant splenectomy with OLTx. These patients were compared to 147 randomly selected OLTx patients without splenectomy within the same time period. One-year patient and graft survival (PS and GS) were lower in splenectomized (Splx) patients compared to nonsplenectomized (non-Splx) patients (59% vs 86% PS, 55% vs 80% GS, respectively). One-month and one-year patient mortality in the Splx group was higher than in the non-splx patients (20% vs 3.4%, $P < 0.001$ for one month; 40% vs 14.3%, $P = 0.003$ for one year, respectively). One-month and one-year sepsis-related mortality was also high in Splx patients (17.5% vs 2.7%, $P = 0.0022$, for one month, and 30% vs 11.5%, $P = 0.0043$, for one year, respectively). We conclude that concomitant splenectomy with OLTx has a significantly higher patient mortality mainly due to its septic complications and, at present, unless there is a specific indication for a splenectomy, the routine addition of this procedure to liver allograft surgery would not be recommended.

**KEY WORDS:** liver transplantation; splenectomy; rejection; sepsis.

There are contradictory reports regarding the effect of splenectomy on allograft rejection following transplantation (1–14). Some have reported a beneficial effect of splenectomy either pre- or peritransplantation (1–4, 6, 7, 9, 10) and have attributed this benefit to a reduction in antibody production (1, 2) or improved leukocyte count and therefore tolerance to azathioprine (AZA) (3, 4, 6, 10, 15). Others have shown no benefit, discouraging the routine use of this procedure because of its potentially lethal complications due to delayed infection and thromboembolic events (5, 8, 13, 16).

Because of the nearly universal presence of pancytopenia in seriously ill liver candidates and consequent problems with AZA dosing, concomitant splenectomy was performed with liver transplantation in most hepatic recipients until 1980. With the advent of nonmyelotoxic agents, such as cyclosporine, the routine use of this frequently difficult adjuvant procedure was discontinued and is rarely performed today.

The objective of our study was to examine the role of splenectomy in liver transplantation and to identify

Manuscript received May 7, 1998; revised manuscript received May 7, 1998; accepted May 11, 1998.

From the Thomas E. Starzl Transplant Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213.

Dr. Samimi's current address: Department of Surgery Section of Transplantation Surgery, The Lankenau Hospital, 100 Lancaster Avenue, Wynnewood, Pennsylvania 19096.

Address for reprint requests: Dr. John J. Fung, Department of Surgery, 3601 Fifth Avenue, 4C Falk Clinic, Pittsburgh, Pennsylvania 15213.



0163-2116/98/0900-1931$15.00/0 

TABLE 1. RECIPIENT CHARACTERISTICS

| | *Splenectomized* | | *Nonsplenectomized* | | |
|---|---|---|---|---|---|
| | N | *(%)* | N | *(%)* | P |
| Number | 40 | | 147 | | |
| Age (mean ± SD) | 44.9 ± 10.3 | | 45.4 ± 11.7 | | 0.810 |
| Sex | | | | | |
| Male | 22 | (55.0) | 90 | (61.2) | 0.476 |
| Female | 18 | (45.0) | 57 | (38.8) | |
| Etiology of liver disease | | | | | |
| Viral | 9 | (22.5) | 25 | (17.0) | 0.497 |
| Tumors | 5 | (12.5) | 14 | (9.5) | |
| Biliary | 10 | (25.0) | 29 | (19.7) | |
| Others | 16 | (40.0) | 79 | (53.7) | |
| Positive lymphocytotoxic cross-match* | 10/38 | (26.3) | 23/144 | (16.0) | 0.141 |
| Immunosuppression | | | | | |
| Azathioprine | 13 | (32.5) | 35 | (23.8) | 0.265 |
| Cyclosporine | 26 | (65.0) | 69 | (46.9) | 0.128 |
| FK506 | 13 | (32.5) | 72 | (49.0) | |
| Rescue FK506 | 1 | (2.5) | 6 | (4.1) | |
| Prednisone | 40 | (100.0) | 146 | (99.3) | 1.000 |
| PRA† | | | | | |
| 0% | 23 | (63.9) | 98 | (69.5) | 0.083 |
| 0–29% | 4 | (11.1) | 27 | (19.1) | |
| ≥30% | 9 | (25.0) | 16 | (11.3) | |
| RBC transfusion (mean ± SD) | | | | | |
| Total | 43.5 ± 38.3 | | 23.8 ± 26.0 | | 0.001 |
| Intraoperative | 28.6 ± 29.1 | | 18.2 ± 22.1 | | 0.017 |
| Perioperative | 14.7 ± 21.3 | | 5.5 ± 7.0 | | 0.008 |
| Platelet count (mean ± SD) | | | | | |
| Preoperative | 133.2 ± 83.6 | | 138.0 ± 102.4 | | 0.850 |
| Postoperative | 292.2 ± 254.7 | | 257.1 ± 139.8 | | 0.784 |
| UNOS status‡ | | | | | |
| 1 and 2 | 7 | (20.0) | 33 | (23.6) | 0.789 |
| 3 | 13 | (37.1) | 46 | (32.9) | |
| 4 | 6 | (17.1) | 32 | (22.9) | |
| 4US | 9 | (25.7) | 29 | (20.7) | |

* Lymphocytotoxic cross-match status was not available in five patients: two Splx, three controls.
† PRA was unknown in 10 patients: four Splx, six controls.
‡ UNOS status was unknown in 12 patients: five Splx, seven controls.

the potential hazards associated with this procedure in modern immunosuppressive regimens.

## MATERIALS AND METHODS

The records of 1466 patients who underwent OLTx at the University of Pittsburgh between January 1987 and October 1991 were reviewed. Nineteen patients undergoing upper abdominal exenteration and thirteen patients with splenectomy (Splx) following OLTx were excluded from this study. From the remaining 1434 patients, we identified 40 (2.8%) who had undergone combined OLTx + Splx. The course of these patients was compared to 150 randomly selected non-Splx patients from the same transplant period. The sample size was calculated to ensure that a 25% or more difference in mortality could be detected between the Splx and the non-Splx group using methods of unequal group sizes (17). The records of three patients could not be obtained, therefore, the remaining 147 patients served as the non-Splx group. The two groups were comparable with respect to donor and recipient age, sex, HLA-A, B, and DR mismatch, etiology of liver disease, UNOS status, cold ischemic time, platelet count, and immunosuppressive regimen (Tables 1 and 2). Although there were more positive lymphocytotoxic cross-matches in the study (Splx) group, the difference was not statistically significant (Tables 1 and 2). The two groups were not comparable with respect to the amount of perioperative blood transfusion.

Indications for splenectomy included positive lymphocytotoxic cross-match, ($N$ = 10), portosystemic shunts [distal splenorenal shunt ($N$ = 10), portocaval shunt ($N$ = 1)], technical complications ($N$ = 10), and distal pancreatic tumor resection ($N$ = 2). In seven patients the reason for Splx could not be determined in the retrospective review (Table 3).

The two groups were analyzed with respect to patient and graft survival, as well as biopsy-proven acute allograft rejection within 30 days of transplantation.

TABLE 2. DONOR CHARACTERISTICS

| | *Splenectomized* | *Nonsplenectomized* | P |
|---|---|---|---|
| Age (mean ± SD) | 27.1 ± 11.1 | 29.2 ± 13.5 | 0.371 |
| Cold ischemia time (mean ± SD) | 12.9 ± 6.0 | 13.4 ± 5.1 | 0.607 |
| HLA-A, B, DR Matches | | | |
| 0 | 13 (48%) | 64 (59%) | 0.289 |
| 1 | 14 (52%) | 41 (38%) | |
| 2 | 0 | 4 (4%) | |
| Mismatches | | | |
| 0 | 3 (11%) | 16 (15%) | 0.176 |
| 1 | 17 (67%) | 47 (43%) | |
| 2 | 7 (26%) | 46 (42%) | |

**Statistical Analysis.** The results for continuous variables are presented as means ± SD and for categorical variables as proportions. The standard two-sample *t* test was used to test the difference between group means, while differences in proportions were tested using Pearson's chi-square test or Fisher's exact test. The Wilcoxon rank-sum test, a nonparametric equivalent to the standard two-sample *t* test, was used for highly skewed data (eg, amount of blood transfusions and platelet count). The odds ratio was calculated as an estimate of the relative risk of acute allograft rejection for Splx patients. An odds ratio >1 indicates increased risk, while an odds ratio <1 indicates a protective effect of splenectomy. The Mantel-Haenszel procedure (18) was used to calculate an adjusted odds ratio based on lymphocytotoxic cross-match. A multivariate logistic regression model was used to adjust the odds ratio for amount of blood transfusions. The 95% confidence intervals were calculated using either the test-based procedure of Miettinen or Woolf's method (18).

Patient survival was calculated from the date of OLTx until death, and graft survival from the date of OLTx until retransplantation or patient death. Survival curves were generated using the Kaplan-Meier (product-limit) method and were compared using the generalized Wilcoxon (Breslow) test. All tests were two-tailed. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS for Windows software.

TABLE 3. INDICATION FOR SPLENECTOMY AND ASSOCIATED MORTALITY AT 30 DAYS

| | | | *Mortality* | |
|---|---|---|---|---|
| | N | % | N (%) | P |
| Positive lymphocytotoxic cross-match | 10 | 26.3 | 4 40 | 0.093† |
| Negative lymphocytotoxic cross-match | 28 | 73.7 | 4 14.3 | |
| Distal splenorenal shunt (DSRS) | 10 | | 0 | |
| Portocaval shunt | 1 | | 1 | |
| Technical* | 8 | | 0 | |
| Pancreatic tumor | 2 | | 0 | |
| Unidentified | 7 | | 3 | |
| Total | 38* | | | |

* Cross-match status unknown in two patients.
† Fisher's exact test.

## RESULTS

**Patient Survival.** With a minimum follow-up of one year (median 35, range 12–17 months), the one-year patient survival was 60% (24/40) in the Splx group vs 86% (126/147) in the non-Splx group ($P = 0.001$), a disparity that was already significant at 30 days ($P = 0.001$) (Figure 1).

In the Splx group, eight patients died within 30 days of OLTx (8/40, 10%) compared to five in the non-Splx group (5/147, 3%, $P < 0.0001$). Four of the eight deaths were in patients with a positive cross-match (4/10, 40%) and the other four in patients with negative cross-match (4/28, 14%, $P = 0.093$) (Table 3). The one-year mortality based on positive cross-match was 60% (6/10) in the Splx group and 22% (5/23) in the non-Splx group ($P = 0.0037$). The one-year mortality based on negative cross-match was 36% (10/28) in the Splx group and 12% (15/121) in the non-Splx group ($P = 0.005$).

Seven of the eight deaths in the Splx group during the first month (7/40, 17.5%) as well as 12 of the 16 by the end of the first year (12/40, 30%) were due primarily to sepsis compared to 4/147 (2.7%, $P = 0.0022$) and 17/147 (11.6%, $P = 0.0043$), in the non-Splx group, respectively.

Three of the 40 (7.5%) patients in the Splx group, including two cross-match-positive patients, underwent retransplantation within 30 days of OLTx because of either primary nonfunction (PNF, $N = 1$) or hepatic artery thrombosis (HAT, $N = 2$). One more patient was retransplanted after 30 days, for a total incidence of 10%. Two (50%) of the four attempts succeeded. Fourteen (9.5%) patients in the non-Splx group also underwent retransplantation, including three with a positive cross-match liver. Eight (57%) were successful.

**Graft Survival.** With the equivalent rate of successful retransplantation, the graft survival curves of the Splx and non-Splx groups were both 5% lower than patient survival, and similar at all time points. Graft survival for Splx at one month was 78% vs 93% for non-Splx ($P = 0.004$), and at one year was 55% vs 80%, respectively ($P = 0.001$).

**Multivariate Analysis.** Using a multivariate logistic regression analysis, Splx patients had a higher risk of one year mortality (odds ratio = 3.1, $P = 0.042$) even after adjusting for selected baseline recipient and donor characteristics. However, this multivariate analysis did not reveal a significant association between splenectomy and graft failure at one year.

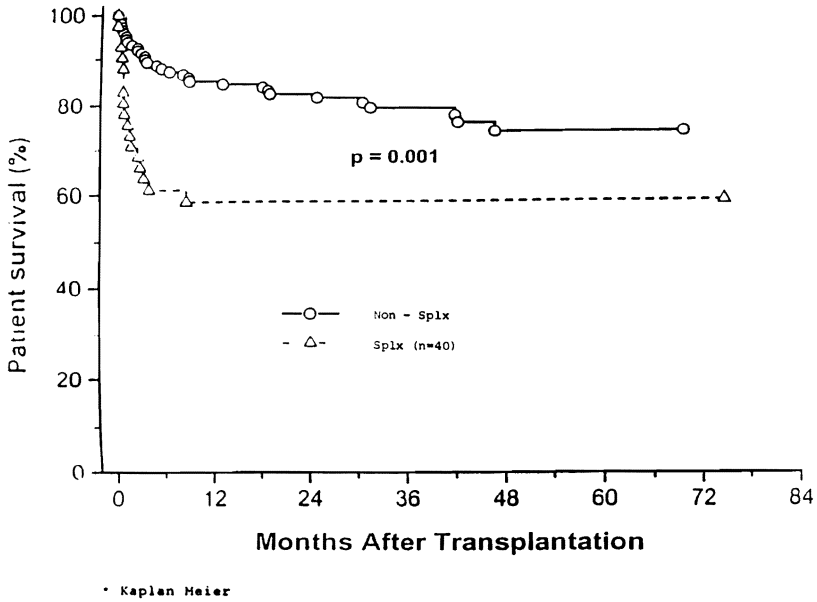


**Fig 1.** Orthotopic liver transplantation between January 1987 and October 1991. Kaplan-Meier patient survival. Graft survival in both cohorts was 5% lower (the retransplantation factor) but otherwise was essentially identical.

**Rejection.** The incidence of acute allograft rejection one month following OLTx was significantly lower in the Splx group (20/40, 50%) compared to the non-Splx group (108/147, 74%, $P = 0.005$), an advantage seen with and without a positive lymphocytotoxic cross-match (Table 4).

The Splx patients received significantly more units of blood transfusion within one month of OLTx than non-Splx patients (Table 1); however, in a multivariate logistic regression model, the rejection rate was not affected by the difference in the total amount of blood transfusions (Table 5).

## DISCUSSION

The contribution of the spleen as part of the immune response to the transplanted graft is not clearly known (6, 19–22). The spleen is not only the principle site of antibody synthesis (6, 9, 23), including specific alloantibodies (22, 24–26), but also is a source of

TABLE 4. INCIDENCE OF ACUTE REJECTION ONE MONTH AFTER LIVER TRANSPLANTATION*

| | *Splenectomized* | *Nonsplenectomized* | *Odds ratio* | P |
|---|---|---|---|---|
| One month | 20/40 (50.0%) | 108/147 (73.5%) | 0.361 | 0.005 |
| By lymphocytotoxic cross-match† | | | | |
| Positive | 4/10 (40.0%) | 19/23 (82.6%) | 0.140 | 0.035‡ |
| Negative | 15/28 (53.6%) | 88/121 (72.7%) | 0.433 | 0.048 |

*Test for homogeneity of the odds ratio: $P = 0.263$; Mantel-Haenszel estimator of the common odds ratio = 0.340; 95% confidence interval = 0.161–0.715.
† Cross-match status unknown in five patients: two Splx, three controls.
‡ Fisher's exact test.

TABLE 5. ESTIMATED RISK OF ACUTE REJECTION FOR SPLENECTOMIZED PATIENTS ADJUSTED FOR AMOUNT OF BLOOD TRANSFUSED ONE MONTH AFTER TRANSPLANTATION

| | *Odds ratio univariate* | *95% confidence limits* | | P | *Adjusted odds ratio multivariate* | *95% confidence limits* | | P |
|---|---|---|---|---|---|---|---|---|
| | | *Lower* | *Upper* | | | *Lower* | *Upper* | |
| Splenectomy | 0.361 | 0.176 | 0.742 | 0.005 | 0.361 | 0.170 | 0.770 | 0.008 |
| Blood transfusion (total) | | | | 0.997 | 0.987 | 1.008 | 0.633 | |

specific alloreactive host lymphocytes (23). It has been suggested that transient posttransplant migration of dendritic cells from the transplanted graft to the spleen may be responsible for initiation of graft rejection (20). On the contrary the spleen may play a major role in prolongation of graft survival in different species (19, 21, 23, 27–29), perhaps by generation of specific suppressor cells (30).

Starzl et al (1) were first to suggest the role of splenectomy in prolongation of allograft survival, as four of their five patients treated by thymectomy and splenectomy maintained their renal function for almost six months. Hume et al (3) suggested that splenectomy, if done prior to or at the time of transplantation, could improve leukocyte count and permit administration of large doses of AZA. A report by Gleason and Murray (4), also noted the advantage of splenectomy but only in living related kidney transplant patients. Two reports in the 1980s also noted improved patient and graft survival after splenectomy (7, 8). This is in contrast to several reports in the late 1980s that have cautioned against the routine use of splenectomy in the renal transplant population (9, 10, 14, 16, 31, 32).

This retrospective study was undertaken because of the concern that decisions to perform urgent splenectomy were made only for its historical justification, namely, the mitigation of the spleen-dependent antibody response (25, 26, 33–35), without attention to its hazards.

Our concern about splenectomy is similar to those that have been experienced in renal transplantation. A common theme in the earlier studies was that splenectomy appeared to reduce the incidence of early rejection (4, 7, 8). Similar to the report by Megison (36), Splx patients in our study had a significantly lower rate of rejection compared to non-Splx patients. This difference was still apparent when rejection was stratified by positive and negative lymphocytotoxic cross-match (Table 3). Patients with positive cross-matches may present with a clinical picture of antibody-mediated rejection indistinguishable from PNF (37); however, in our study none of the retransplanted patients for PNF had any histologically documented acute rejection.

In our study splenectomy was associated with more blood transfusion. This extra transfusion requirement could be due to unexpected injury to the spleen or may be the result of preformed lymphocytotoxic antibody, which may lead to excessive elimination of platelets and subsequent hemorrhage (38).

The most emphasized risk of splenectomy in the literature is the increased susceptibility to infection and thrombotic complications. However, in our opinion, the most serious hazard of splenectomy in a liver recipient is aggravation of an already difficult technical operation.

Nevertheless, splenectomy independent of other factors, including blood transfusion, has been associated with an increased risk of mortality (16), with sepsis as the leading cause. Our concern is reinforced by the study reported here and emphasizes that the price of this extra surgical procedure far outweighs any theoretical benefits in OLTx patients. We conclude that, based on multiple life-threatening risk factors associated with splenectomy, concomitant splenectomy with OLTx is not recommended except in the rare occasion of unavoidable splenic injury.

Instead of splenectomy for patients with a positive cytotoxic cross-match, we now recommend intraoperative treatment with a combination of high-dose corticosteroids and prostaglandin $E_1$. This treatment is thought to ameliorate the diffuse inflammatory response that is the basis of hyperacute rejection or its subclinical variations (39, 40). Since instituting this management policy in 1992 (41), the extra hazard of liver transplantation in the case of a positive crossmatch (40, 42) has been all but eliminated (43).

## SUMMARY

The single center experience with splenectomy in OLTx patients has been reviewed. One thousand four hundred sixty-six patients had OLTx over a period of five years. Forty of these patients had splenectomy at the time of OLTx. These patients were compared to a randomly selected group of OLTx patients who did not have splenectomy within the same time period. The results demonstrate that splx patients are at increased risk for mortality, independent of other factors, mainly a due to increased sepsis-related complications.

## REFERENCES

1. Starzl TE, Marchioro TL, Talmage DW, Waddell WR: Splenectomy and thymectomy in human renal homotransplantation. Proc Soc Exp Biol Med 113:92, 1963
2. Starzl TE: Role of excision of lymphoid masses in attenuating the rejection process. *In* Experience in Renal Transplantation. Starzl TE (ed). Philadelphia, WB Saunders 1964, 126
3. Hume DM, Magee JH, Kauffman HM, Bower JD, Lee HM, Cleveland RJ, Prout GR: Transplantation results at the Med-

ical College of Virginia. Summary through September 1963. Transplantation 2:164, 1964
4. Gleason RE, Murray JE: Report from kidney transplant registry: Analysis of variables in the function of human kidney transplants I. Blood group compatibility and splenectomy. Transplantation 5:343, 1967
5. Pierce JC, Hume DM: The effect of splenectomy on the survival of first and second renal homotransplants in man. Surg Gynecol Obstet 127:1300–1306, 1968
6. Krivit W, Giebink GS, Leonard A: Overwhelming postsplenectomy infection. Surg Clin North Am 59:223, 1979
7. Stuart FP, Reckard CR, Ketel BL, Schulak JA: Effect of splenectomy on first cadaver kidney transplants. Ann Surg 192:553, 1980
8. Fryd DS, Sutherland DER, Simmons RL, Ferguson RM, Rjellstrand CM, Najarian JS: Results of a prospective randomized study on the effects of splenectomy versus no splenectomy in renal transplant patients. Transplant Proc 13:48, 1981
9. Peters TG, Williams JN, Harmon HC, Britt LG: Splenectomy and death in renal transplant patients. Arch Surg 118:795, 1983
10. Lewis RM, Banowsky LHW, Nicastro-Lutton JJ, Cruz AB, Saunders PH: Selective post transplant splenectomy in recipients of cadaveric renal allografts. Transplantation 36:198, 1983
11. Mozes MF, Spigos DG, Thomas PA, Nisikawa RA, Cohen C, Johnasson O: Antilymphocyte globulin (ALG) and splenectomy or partial splenic embolization (PSE): Evidence for a synergistic beneficial effect on cadaver renal allograft survival. Transplant Proc 15:613, 1983
12. Krakauerr H, Spees EK, Vaughn WK, Grauman JS, Summe JP, Bailey RC: Assessment of prognostic factors and projection of outcomes in renal transplantation. Transplantation 36:372, 1983
13. Zincke H, Engen DE, Sterioff S, McDonald MW, Frohnert PP, Johnson WJ: Improving results in primary diabetic renal transplantation. Transplant Proc 16:372, 1984
14. Alexander JN, First MR, Majeski JA, Munda R, Fidler JP, Morris MJ, Suttman MP: The late adverse effect of splenectomy on patient survival following cadaveric renal transplantation. Transplantation 37:467, 1984
15. Lebeau G, Yanaga K, Marsh JW, Tzakis AG, Makowka L, Gordon RD, Todo S, Stieber AC, Iwatsuki S, Starzl TE: Analysis of surgical complication after 397 hepatic transplantations. Surg Gynecol Obstet 170:317, 1990
16. Sutherland DER, Fryd DS, SO SKS, Bentley FR, Ascher NL, Simmons RL, Najarian JS: Long-term effects of splenectomy versus no splenectomy in renal transplant patients. Reanalysis of a randomized prospective study. Transplantation 38:619, 1984
17. Lemeohow S, Hosmer DW, Klor J, Lwanga SK: Adequacy of Sample Size in Health Studies, New York, Wiley 1990
18. Kahn L, Sempos C: Statistical Methods in Epidemiology, New York, Oxford University Press, 1989, p 85
19. Lende M, Santiago-Delphin EA, Lavergne J: Immunobiological consequences of splenectomy: A review. J Surg Res 40:85, 1986
20. Austyn JM, Kupiec-Weglinski JW, Hankins DF, Morris PJ: Migration patterns of dendritic cells in the mouse. J Exp Med 167:646, 1988
21. Meiser BM, Morris RE: The importance of the spleen for the immunosuppressive action of cyclosporine in transplantation. Transplantation 51:690, 1991
22. Shaked A, Busutti RW: Liver transplantation in patients with portal vein thrombosis and central portocaval shunts. Ann Surg 214:696, 1991
23. Yamaguchi Y, Halprin EC, Harland RC, Wyble C, Bollinger RR: Significant prolonging of hamster liver transplant survival in Lewis rats by total lymphoid irradiation, cyclosporine, and splenectomy. Transplantation 49:13, 1990
24. Monden M, Valdivia LA, Gotoh M, Kubota N, Hosuike Y, Nakano Y, Okamura J, Mori T: A crucial effect of splenectomy on prolonging cardiac xenograft survival in combination with cyclosporine. Surgery 105:535, 1989
25. Jiang H, Takahara S, Kyo M, Hashimoto M, Takano Y, Kameoka H, Moutabarik A, Kokado Y, Ishibashi M, Okuyama A, Sonoda T: Prolonged cardiac allograft survival in sensitized rats by low-dose FK506 in combination with splenectomy. Transplant Proc 23:3291, 1991
26. Johnson EM, Fischel RJ, Boyle EM, Matas AJ, Bolman RM: Plasma exchange, splenectomy, and cyclophosphamide for natural antibody removal: Kidneys and xenograft survival. Transplant Proc 24:701, 1992
27. Yamaguchi Y, Halperin EC, Harland RC, Wyble C, Bollinger RR: Significant prolonging of hamster liver transplant survival in Lewis rats by total lymphoid irradiation, cyclosporine, and splenectomy. Transplantation 49:13, 1990
28. Araneda D, Carobbi A, Thomas J, Thomas F: Paradoxical effects of xenografts in the nude rat: Effects of splenectomy on aberrant graft rejection. Transplant Proc 24:195, 1992
29. Carobbi A, Araneda D, Quarantilo P, Thomas JM, Thomas FT: Synergism of splenectomy and immunosuppressive drugs in prolonging of cardiac xenograft survival. Transplant Proc 24:527, 1992
30. Lim SML, Kohno H, White DJG: Splenectomy abrogates the ability of thorasic duct lymphocyte of tolerant rats to transfer suppression. Transplant Proc 21:480, 1989
31. Rai GS, Wilkinson R, Taylor RMR, Uldall PR, Derr DN: Adverse effect of splenectomy in renal transplantation. Clin Nephrol 9:194, 1978
32. Shofer FS, London WT, Lyons P, Simmonian SJ, Burke JF, Jarrel BE, Grossman RA, Barker CF: Adverse effect of splenectomy on the survival of patients with more than one kidney transplant. Transplantation 42:473, 1986
33. Valdivia LA, Monden M, Gotoh M, Hasuike Y, Kubota N, Ichikawa T, Okamura J, Mori T: Prolonged survival of hamster-to-rat liver xenografts using splenectomy and cyclosporine administration. Transplantation 44(6):759–763, 1987
34. Aradeda D, Carobbi A, Patselas T, Thomas F, Thomas J: Timing of splenectomy is critical in prolongation of cardiac xenografts. Transplant Proc 24:523, 1992
35. Murase N, Starzl TE, Demetris AJ, Valdivia L, Tanabe M, Cramer D, Makowka L: Hamster-to-rat heart and liver xenotransplantation with FK506 plus antiproliferative drugs. Transplantation 55:701–708, 1993
36. Megison SM, McMullin ND, Andrews WS: Selective use of splenectomy after liver transplantation in children. J Pediatr Surg 25:881, 1990
37. Starzl TE, Demetris AJ: Differential Diagnosis of Graft Dysfunction in Liver Transplantation, Chicago, Yearbook Medical Publishers, pp 85–99, 1990
38. Demetris AJ, Nakamura K, Yagihashi A, Iwaki Y, Takaya S, Hartman G, Murase N, Todo S, Bronsther O, Manez R, Fung JJ, Iwatsuki S, Starzl TE: A clinicopathological study of human liver allograft recipients harboring performed IgG lymphocytotoxic antibodies. Hepatology 16:671–681, 1992

39. Starzl TE, Lerner RA, Dixon FJ, Groth CG, Brettschneider L, Terasaki PI: Schwartzman reaction after human renal transplantation. N Engl J Med 278:642–648, 1968
40. Starzl TE, Valdivia LA, Murase N, Demetris AJ, Fontes P, Rao AS, Manez R, Marino I, Todo S, Thomson AW, Fung JJ: The biologic basis of and strategies for clinical xenotransplantation. Immunol Rev 141:213–244, 1994
41. Takaya S, Bronsther O, Iwaki Y, Nakamura K, Abu-Elmagd K, Yagihashi A, Demetris AJ, Kobayashi M, Todo Suite 130, Tzakis AG, Fung JJ, Starzl TE: The adverse impact on liver transplantation of using positive cytotoxic crossmatch donors. Transplantation 53:400–406, 1992
42. Takaya S, Iwaki Y, Starzl TE: Liver Transplantation in positive cytotoxic crossmatch cases using FK506, high dose steroids, and prostaglandin $E_1$. Transplantation 54:927–930, 1992
43. Takaya S, Doyle H, Todo S, Irish W, Fung JJ, Starzl TE: Reduction of primary nonfunction with prostaglandin $E_1$ after clinical liver transplantation. Transplant Proc 27:1862–1867, 1995