The Historic Evolution of Intestinal and Multivisceral Transplantation

38

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Introduction

Although the intestine was one of the first organs to be transplanted in animals, it was the last to be successfully transplanted in humans [1]. Such a significant delay reflects the organ structural and immunologic complexity. For many decades, the intestine was considered a forbidden organ because of the enigma of graft-versus-host disease (GVHD) [2, 3]. With extensive preclinical studies, clinical introduction of various immunosuppressive drugs, and more recently better understanding of gut immunity, intestinal transplantation has become technically feasible with increased practicality and durability over the last three decades [4].

This chapter focuses on the multifaceted historic evolution of visceral transplantation with special reference to the pioneer experimental and clinical work triggered by the introduction of new premises, availability of novel immunosuppressive drugs, and innovation of surgical techniques. In addition, the current status of the different types of visceral transplantation is highlighted with new insights for future consideration.

Experimental Visceral Transplantation

Traced back to the pioneer experimental work of the 1912 Nobel Prize winner Alexis Carrel (Fig. 38.1a), the modern history of bowel transplantation was signaled by the innovative experimental work of Lillehei (Fig. 38.1b) and Starzl (Fig. 38.1c) that was published more than half a century ago [5, 6]. Most of the technical aspects of these canine procedures were the same as those in clinical use today (Fig. 38.2). These experimental models also highlighted some of the immunological and metabolic behavior of the visceral allograft as intestine alone or combined en bloc with other abdominal organs including the liver.

The Carrel's successful implantation of vascular grafts and performance of several autotransplantations were behind the landmark initial experiment of Lillehei and his colleagues at the University of Minnesota. The designed animal model assessed the physiological response of different degrees of small bowel ischemia. The technical feasibility of reimplantation as an auto or visceral allograft was also examined with special focus on patency of the venous and arterial vasculature [5].

The Starzl's model of "mass homotransplantations of abdominal organs" was introduced to study the behavior of a large denervated homograft in which the lymphatic drainage was interrupted. The boldness of the concept was evident in the cataclysmic postoperative course with a longest survival of 9 days among 19 dogs. However, the experiment observed a great degree of functional preservation of the liver that suggests mitigation of the rejection process. The same observation has been recently documented in humans by the senior author [4, 7–9].

Visceral Transplantation in Humans

Isolated Intestine Transplantation

The successful development of clinical intestinal and multivisceral transplantation is one of the most important milestones in modern history of organ transplantation. Five years after the Lillehei experiment, Deterling at the Boston Floating Hospital [10] performed the first small bowel transplant in an infant by using a segment of the mother's ileum.

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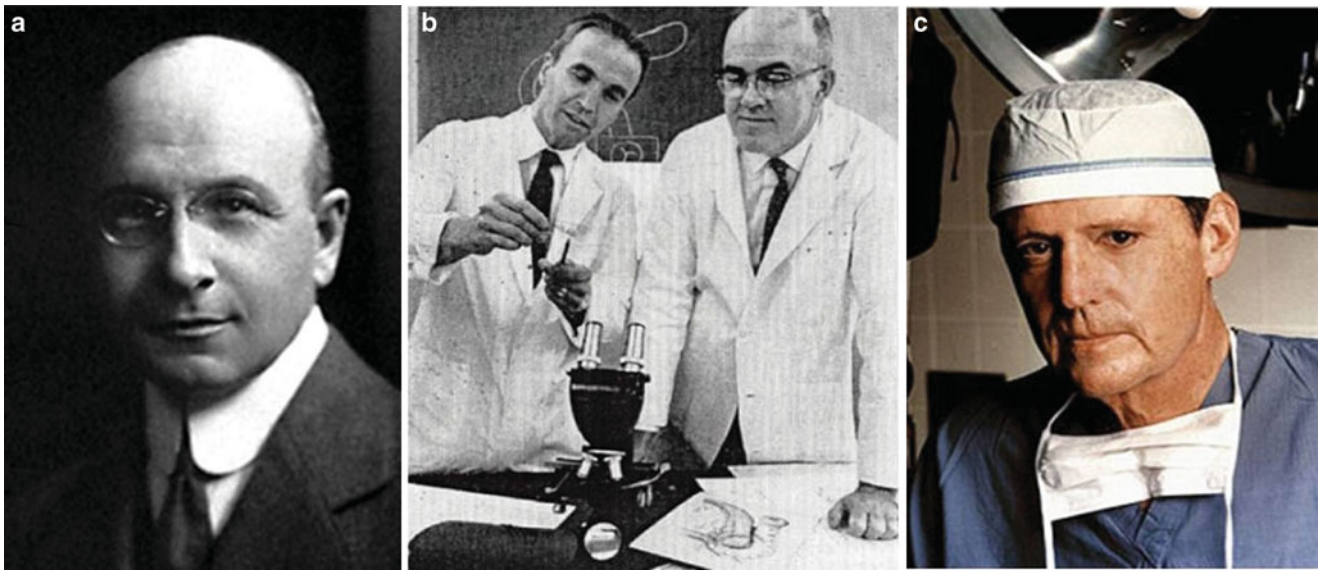

Fig. 38.1 (**a**) Alexis Carrel, (**b**) Richard Lillehei (*left*) and William Kelly (*right*), (**c**) Thomas Starzl

Another intestinal transplant in a child was also declared for the first time by Deterling during the discussion of Alican's first clinical case at the eleventh annual meeting of the society for surgery of the alimentary tract in 1970 [10]. With azathioprine (Imuran) being the primary immunosuppressive agent, the attempts of these innovative surgeons and others across the globe (Fig. 38.3) were short lived with a patient survival ranging from 12 h to a few weeks (Table 38.1) [10–14].

With the late 1970s arrival of cyclosporine, further worldwide attempts were made in humans after good results in rodent animal models. With 13 publications in the English literature (Table 38.2) [13, 15–21], better survival was observed compared to the azathioprine era. Of these recipients, only one patient is currently alive with fully functioning graft for nearly 25 years.

The clinical introduction of FK-506 (currently known as tacrolimus) in 1989 refueled the interest of the transplant community in the field of intestinal transplantation. The early successful outcome with the first isolated intestinal transplantation and subsequent cases under tacrolimus-steroid-based immunosuppression proved the technical feasibility and practicality of intestinal transplantation under tacrolimus as a powerful immunosuppressive agent [22]. The initial encouraging results and continual improvement in outcome will be further discussed under current status of the procedure.

Composite Visceral Transplant

Twenty years after his first successful canine multivisceral transplant experiment, Starzl performed the first multivisceral transplant in humans in 1983 with en bloc inclusion of the stomach, duodenum, pancreas, intestine, and liver [23]. His enthusiasm was stimulated by the clinical availability of cyclosporine as a better immunosuppressive drug. Despite the painful operative experience with the first case, the recipient of the second transplant survived more than 6 months with fully functioning graft to die from progressive post-transplant lymphoproliferative disease (PTLD). Similar attempts were made worldwide under cyclosporine with a patient survival ranging from 7.5 to 66 months (Table 38.3) [23–26]. The procedure has been increasingly utilized in the tacrolimus era [4, 27].

Shortly before the clinical introduction of tacrolimus, Grant et al. published the first case of successful combined liver and intestinal transplantation under cyclosporine in humans [24]. To overcome the observed prohibitive risk of intestinal allograft rejection under cyclosporine, the Ontario group transplanted both the liver and intestine from the same donor to a recipient with normal native liver. Such a successful outcome combined with the clinical introduction of tacrolimus stimulated a wave of enthusiasm that increased the utilization of the different types of intestinal transplantation for patients with irreversible intestinal failure and complex abdominal pathology.

Evolution of Immunosuppression

The clinical introduction of tacrolimus ushered in a new era in the field of intestinal and multivisceral transplantation. Soon after the initiation of the clinical trial with tacrolimus and steroid-based immunosuppression (type I), most centers experienced prohibitive risk of allograft rejections. During such an exciting era, different novel approaches were also introduced due to the introduction of new immunosuppressive agents with new insights into the mechanism of allograft acceptance and transplant tolerance.

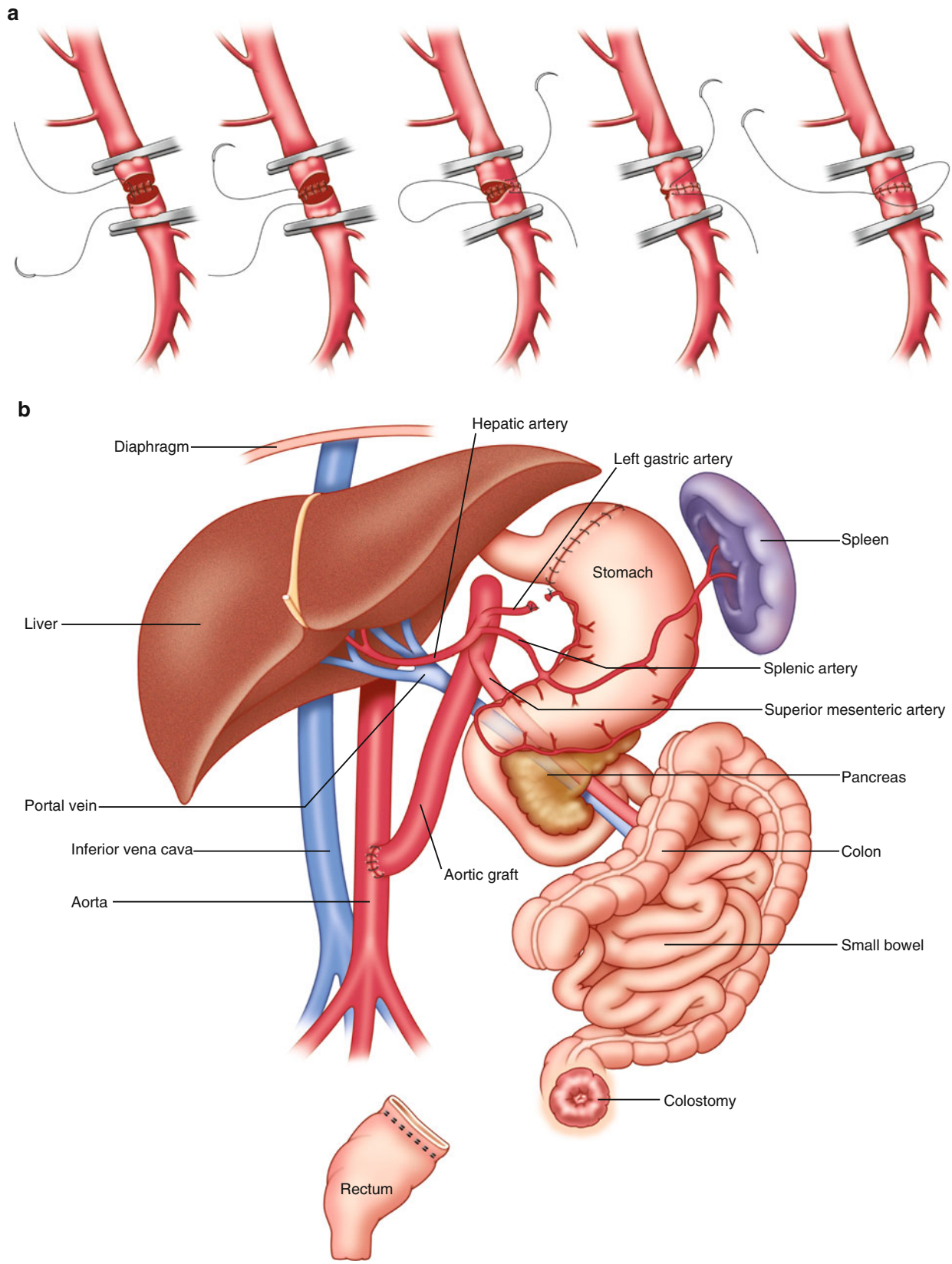

Fig. 38.2 (**a**) Technique for anastomosing the superior mesenteric vessels [5]. (**b**) Schematic view of the transplanted tissues and their anatomic relation to the host

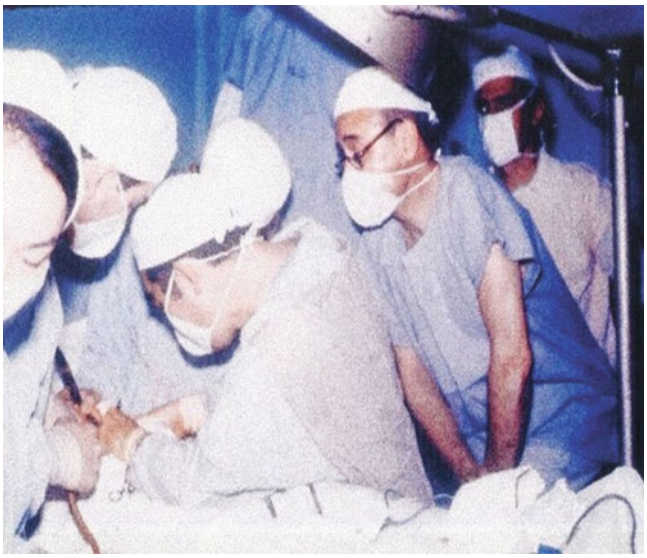

Fig. 38.3 Masayuki Okumura performing the first small bowel transplant in Latin America at the University Hospital of Sao Paulo Brazil in 1968

Table 38.1 Clinical intestinal transplantation in the azathioprine era

Year	Author	Institution	Etiology of intestinal failure	Graft survival
1964	Deterling [10]	Boston Floating Hospital	Mesenteric thrombosis	12 h
1964	Deterling [10]	Boston Floating Hospital	Mesenteric thrombosis	2 Days
1967	Lillehei [11]	University of Minnesota	Intestinal infarction	A few hours
1968	Okumura [12]	University Hospital-Sao Paulo Brazil	Mesenteric thrombosis	10 Days
1969	Olivier [14]	Hôtel-Dieu de Paris	Gardner's syndrome	23 Days
1969	Alican [10]	University of Mississippi	Strangulation by a mesenteric band	9 Days
1969	Okumura [12]	University Hospital-Sao Paulo Brazil	Volvulus	5 Days
1970	Fortner [13]	Memorial Sloan Kettering	Gardner's syndrome	79 Days

Table 38.2 Clinical intestinal transplantation in the cyclosporine era

Year	Author	Institution	Etiology of intestinal failure	Graft survival
1985	Cohen [13]	Toronto General Hospital	Gardner syndrome	10 Days
1987	Tattersall [15]	Rush University, Chicago, USA	Short bowel syndrome	13 Days
1987	Goulet [16]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	8 h
1987	Goulet [16]	Hôpital Necker-Enfants Malades, Paris, France	Volvulous	6 Month
1987	Deltz [17]	University of Kiel, Federal Republic of Germany	Volvulous	12 Days
1988	Goulet [16]	Hôpital Necker-Enfants Malades, Paris, France	Volvulous	17 Months
1988	Grant [18]	University of Western Ontario, London, Canada	Intestinal pseudo-obstruction	14 Days
1988	Deltz [19]	University of Kiel, Federal Republic of Germany	SMV thrombosis	49 Month
1989	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	
1989	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	2 Months
1989	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	24 Days
1989	Wallander [21]	University Hospital, Uppsala, Sweden	Aganglionosis	8 Weeks
1990	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Intestinal atresia	7 Months

Table 38.3 Clinical transplantation of composite visceral grafts

Year	Author	Institution	Etiology of intestinal failure	Graft survival
1983	Starzl [23]	University of Pittsburgh Medical Center	Short bowel syndrome + liver failure	A few hours
1986	Williams [25]	Rush-Presbyterian-St Luke's Medical Center	Gastroschisis + liver failure	4 Days
1987	Starzl [23]	University of Pittsburgh Medical Center	Neonatal volvulus + liver failure	192 Days
1988	Williams [25]	Rush-Presbyterian-St Luke's Medical Center	Volvulus + liver failure	109 Days
1988	Grant [24]	University of Western Ontario	Short bowel syndrome	
1989	Margreiter [26]	Innsbruck Medical University	Cancer (head of the pancreas)	8 Months

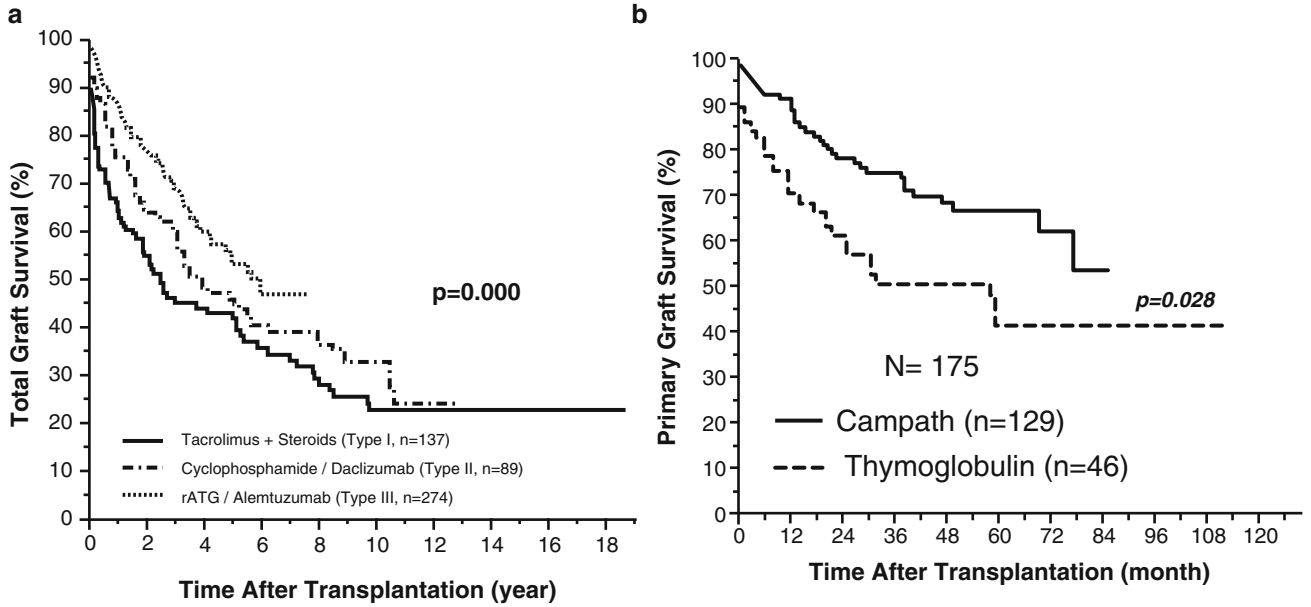

Fig. 38.4 (**a**) Improvement of visceral allograft survival according to the type of immunosuppression. (**b**) Better graft survival in patients pretreated with alemtuzumab (Campath-1H) compared to those pretreated with antithymocyte globulin (thymoglobulin) (data from Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg 2009;250(4):567–81; and Abu-Elmagd KM, Costa G, Bond GJ, et al. A decade of experience with a single dose of rabbit antithymocyte globulin or alemtuzumab pretreatment for intestinal and multivisceral transplantation. Clin Transpl 2012:155–66)

With more emphasis on the difficulty of clinical care rather than survival, induction therapy with cyclophosphamide and daclizumab was introduced as part of multiple-drug immunosuppression including different cellular and molecular targets (type II) (Fig. 38.3). With better control of rejection, the overall survival has improved at major centers and according to the Intestinal Transplant Registry (ITR) [4, 28–30]. Unfortunately, updated results confirmed the long-term detrimental effect of chronic multiple-drug maintenance immunosuppression with erosion of the observed early survival benefits beyond the 10-year post-transplant landmark [4] (Fig. 38.4a).

With new insights into the mechanism of allograft acceptance and transplant tolerance, recipient preconditioning using thymoglobulin or alemtuzumab (Campath-1H) (Fig. 38.4b) with post-transplant minimal immunosuppression was introduced (type III) with the aim to improve allograft stability and reduce the need for long-term post-transplant immunosuppression at the University of Pittsburgh [31–33]. With perioperative partial depletion of the recipient lymphoid cells, amelioration of the initial donor-specific immune response is expected. Jointly application of minimal post-transplant immunosuppression has the potential to avoid the possible erosion of the alloengraftment mechanism of clonal exhaustion-deletion without high penalty of destructive immune response [32, 33]. The Pittsburgh intestinal and multivisceral recipients were the first to receive such a novel protocol with further improvement in overall

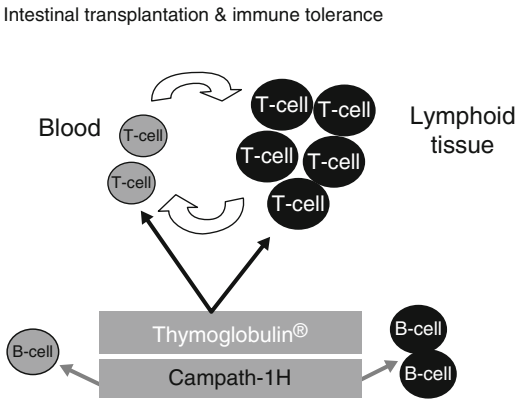

Fig. 38.5 This illustration depicts the dynamics of the lymphocyte depletion by both thymoglobulin (rATG) and Campath-1H (alemtuzumab). Note that both agents are effective in depleting both the intravascular and tissue T-lymphocytes. However, only Campath-1H is effective against the B-lymphocytes

outcome [4]. Reduction in the total incidence of intractable rejection and fatal infections partially contributed to better overall survival. Equally encouraging is the concomitant reduction in risk and fatality of PTLD despite the depletion of recipient lymphoid cells. With such a novel protocol, further improvement in outcome was achieved with more survival advantage utilizing alemtuzumab compared to rabbit antithymocyte globulin (thymoglobulin) (Fig. 38.5) [9]. A similar protocol has been reported by the Miami group utilizing alemtuzumab as an induction and not a pretreatment

agent with multiple perioperative doses with no attempts to space out the tacrolimus maintenance dosage [34, 35].

The demonstrated striking ability to further reduce maintenance immunosuppression with recipient pretreatment supports Pittsburgh's hypothesis of successful induction of partial tolerance in these immunologically challenging recipients. With the unprecedented successful achievement of spaced doses of tacrolimus up to 8 years, partial tolerance is achievable and drug-free long-term engraftment is within reach despite the high intestinal allograft immunogenicity [4, 9].

Improved Outcome

Survival

The cumulative worldwide clinical experience demonstrated steady improvement in one and five actuarial graft survival [32]. However, a time series analysis of conditional 5-year actuarial survival showed only slight improvement over time [36]. Beyond the 5-year milestone, the conditional survival of Pittsburgh series showed a patient survival rate of 75 % at 10 years and 61 % at 15 years, with a graft survival of 59 and 50 %, respectively (Fig. 38.6) [37]. Graft failure and various complications including immunosuppression-related organ injury continued to impact the patient long-term survival with rejection, infection, and renal failure [4].

The long-term survival risk factors are summarized in Table 38.4. Nonfunctional social support and non-inclusion of the liver as part of the visceral allograft were the most significant risk factors of patient survival and graft failure (Fig. 38.7). Non-inclusion of the liver continued to be the most significant predictor of late graft loss since Pittsburg group reported the immune-protective effect of the liver in 1998 [4, 7, 8]. Other significant predictors include early rejection, female recipient, older recipient age, splenectomy, and retransplantation.

Graft Function

The ability to restore nutritional autonomy and other graft functions is the important metric to assess therapeutic efficacy [4]. The reported high rate of long-term nutritional autonomy without intravenous nutrition and the improved body mass index (BMI) with sustained serum albumin levels higher than that before transplantation are testimony of excellent allograft function (Fig. 38.8). In a recently published cross-sectional study on pediatric recipients, positive growth was observed in the majority of cases, particularly those with steroid-free immunosuppression but with limited catch-up [38]. The failure to achieve full functional recovery includes the sustained gut dysmotility and fat malabsorption. These are due to the result of denervation and lymphatic disruption of the visceral allograft, respectively [39].

Quality of Life

With the continual improvement in survival outcome, the health-related quality of life (HRQOL) issues have become an important primary therapeutic index. The relatively young

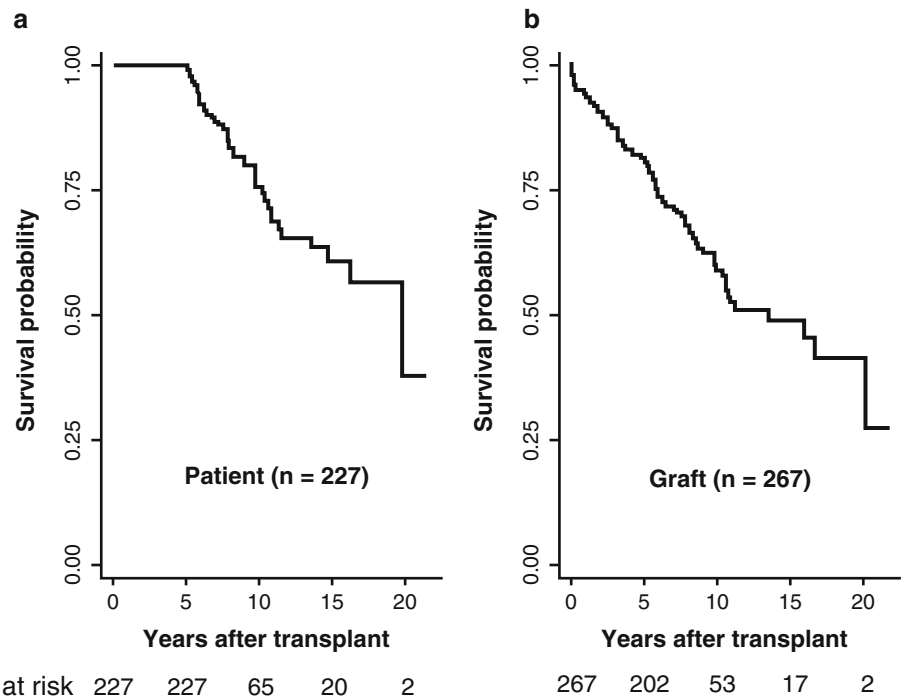

Fig. 38.6 Survival curves for conditional patient (**a**) and graft (**b**) survival after visceral transplantation. The analysis excluded patients who demised before the 5-year post-transplant landmark (data from Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3):494–508)

Table 38.4 Long-term patient and graft survival risk factors

	p	Hazard ratio	95 % Confidence interval
Patient			
Lack of social support	0.000	6.132	3.370–11.160
Rejection ≤90 days	0.016	2.363	1.172–4.765
Female recipient	0.025	1.992	1.089–3.646
Recipient age ≥20 years	0.025	2.014	1.093–3.711
Re-transplantation	0.026	2.053	1.089–3.873
No preconditioning	0.046	2.013	1.013–4.997
Graft			
Liver-free allograft	0.000	3.224	2.026–5.132
Splenectomy	0.001	2.212	1.396–3.506
HLA mismatch	0.040	1.258	1.011–1.565
Rejection ≤90 days	0.046	1.601	1.008–2.541
PTLD	0.085	1.638	0.934–2.872

HLA human leukocyte antigen, *PTLD* post-transplant lymphoproliferative disease
Modified from Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3): 494–508, with permission

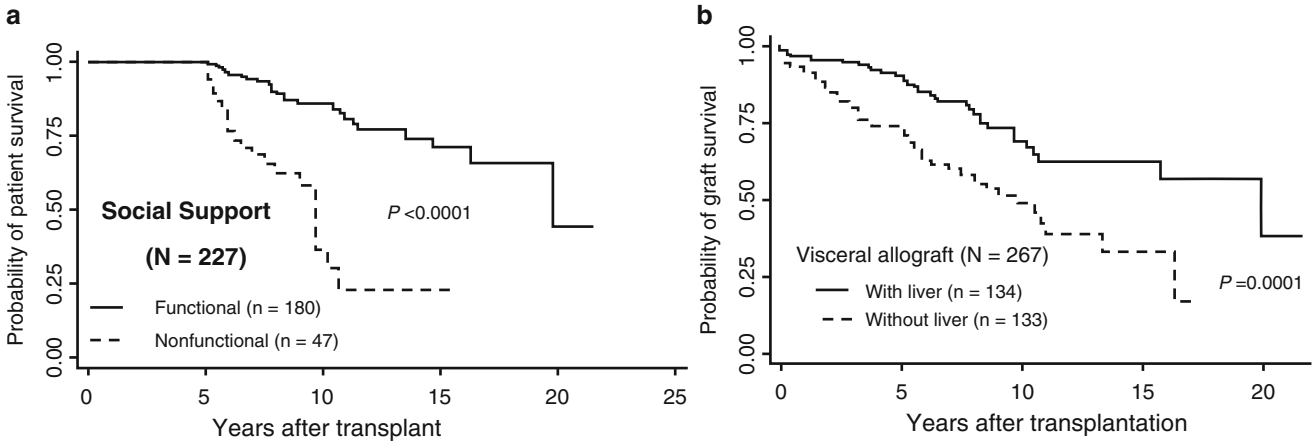

Fig. 38.7 Long-term conditional survival probability for patients according to social support status (**a**) and overall cumulative graft survival according to allograft type, with special reference to inclusion of the liver (**b**). Both variables were the most significant predictors of long-term patient and graft survival, respectively (data from Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3):494–508)

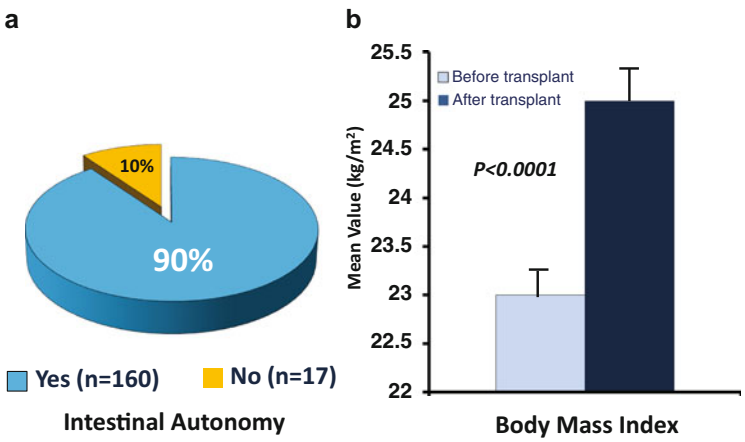

Fig. 38.8 Long-term graft function of 177 visceral allograft recipients who survived beyond 5 years at the University of Pittsburgh Medical Center.
(**a**) Achievement of enteric autonomy defined by freedom from intravenous nutrition and fluid supplement.
(**b**) Body mass index before and after transplantation

clinical age of the field with its multifaceted complexity has limited the validity of the currently available tools to assess HRQOL in this unique population. In addition, the utilization of the procedure as a rescue therapy has negatively biased most of the quality of life measurements.

Several studies addressed the HRQOL following visceral transplantation among both children and adults using different study instruments [4, 28, 37, 40–45]. With the use of the child health questionnaire, two well-designed studies demonstrated physical and psychosocial functions similar to healthy normal children [40, 41]. However, the parental proxy assessments were different from the recipients, with lower response in multiple categories including physical health and social functioning. In addition, lower values among the school functioning subcategories and psychological health summary score were also reported [41].

The HRQOL was addressed in five series of adult recipients that were published in peer-reviewed journals with dedicated study design [37, 43, 45–47]. All of these studies demonstrated improvement in many of the quality of life domains, with a better overall rehabilitative index than HPN including the use of treatment-specific questionnaires [47]. With the exception of depression and increased financial demands, successful transplantation offsets the deprived effect of HPN on most of the QOL domains and resolves the chronicity of the primary disease [37, 46].

The multidimensional quality of life aspects in both adults and children have been recently addressed in a comprehensive single report reflecting the largest single-center experience with more than two decades of follow-up [37]. The study identified, for the first time, a spectrum of different developmental, psycho-neurological, and behavioral disorders among visceral allograft recipients, particularly children, including autism, developmental delay, attention-deficit/hyperactivity disorders, and deafness at a relatively higher rate than the general population [37]. The authors attributed these observations to organic brain dysfunctions that occurred due to intestinal failure during the early phases of neuronal, emotional, and physical development. The disease process is also compounded by the pre-transplant HPN-associated complications and morbidities that may occur after transplant. Of the documented pathologic changes are brain atrophy, cerebral vascular insufficiency due to multiple septic emboli, micronutrient deficiencies, trace element toxicities, and liver failure-induced metabolic encephalopathy [48–54]. Accordingly, early consideration for gut rehabilitation including transplantation is recommended with the aim to reduce the risk of such devastating irreversible deficits particularly among the pediatric population.

The long-term rehabilitative efficacy of visceral transplantation was recently accessed utilizing the socioeconomic milestones [37]. A high education index was reported among all respective age group with sustained cognitive, psychosocial, and physical functions after all types of visceral transplantation. In addition, the ability to create a nuclear family, having children, and becoming a productive citizen is another valid indicator of a high rehabilitative index after visceral transplantation. Equally important is that most recipients scored high on the Lansky and Karnofsky performance scales, with normal functional activities in 88 % of current survivors [55] (Fig. 38.9).

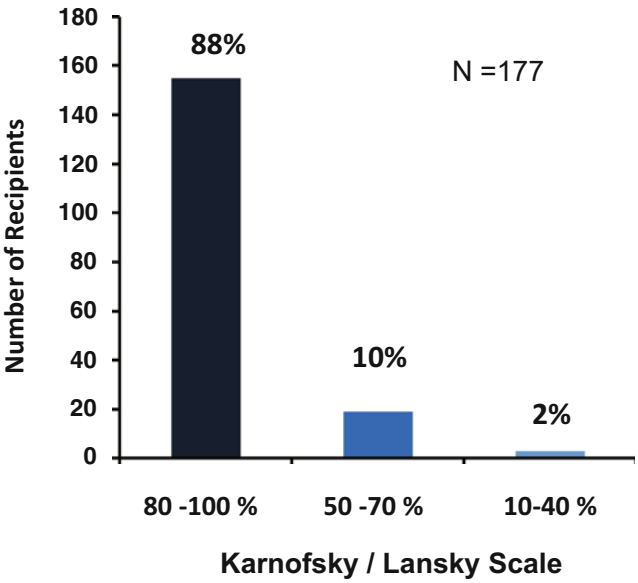

Fig. 38.9 One hundred and fifty-six of 177 (88 %) visceral allograft recipients in University of Pittsburgh Medical Center who survived beyond the 5-year milestone scored 80–100 % on the Lansky/Karnofsky performance scale

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