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Original article

Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome

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SUMMARY

Background & aims: Short bowel syndrome (SBS) is a rare and severe condition where home parenteral nutrition (HPN) dependence can be either permanent or transient. The timing of HPN discontinuation and the survival, according to SBS characteristics, need to be further reported to help plan pre-emptive intestinal transplantation and reconstructive surgery.
Methods: 268 Non-malignant SBS patients have been followed in our institution since 1980. HPN dependence and survival rate were studied with univariate and multivariate analysis.
Results: Median follow-up was 4.4 (0.3–24) years. Actuarial HPN dependence probabilities were 74%, 64% and 48% at 1, 2 and 5 years, respectively. In multivariate analysis, HPN dependence was significantly decreased with an early (<6 mo) plasma citrulline concentration >20 μmol/l, a remaining colon >57% (4/7) and a remnant small bowel length >75 cm. Among the 124 patients who became HPN independent, 26.5% did so more than 2 years after SBS constitution.
Conclusions: This study indicates that long-term HPN is required in 47% of SBS patients started on this therapy. HPN independence is significantly associated with the remnant small bowel length, remaining colon and early plasma citrulline concentration. Noteworthy, HPN dependence could be reversed until 5 years after SBS constitution.

1. Introduction

Intestinal failure (IF) is a highly disabling condition characterized by the inability to maintain protein-energy, fluid, electrolyte and micronutrient balances under a normal unrestricted diet.[1] IF ultimately leads to increasing malnutrition and even death if not circumvented by home parenteral nutrition (HPN).[2] In adult patients, short bowel syndrome (SBS) is the major cause of IF.[3]

In SBS, HPN dependence may be either permanent (or deemed irreversible) or transient.[4] Although it is still debated, the human intestine has an inherent ability to adapt functionally and morphologically after a massive resection, leading to an improvement in its absorptive capacity overtime.[4] These changes are mainly related to increased intraluminal absorption and enteral neuro-hormonal stimuli but also to behavioural changes, mainly spontaneous oral hyperalimentation (adaptive hyperphagia).[5] All these changes aim to ultimately discontinue HPN. Classically, it is accepted that the time to discontinue HPN may be of at least 2 years in adult patients with a colon in continuity.[6] However, late HPN discontinuation has also been described.[7,8] Therefore, the timing of HPN discontinuation, according to the characteristics of the patients and SBS, needs to be further investigated.

HPN has become the standard treatment for IF, offering a long-term survival demonstrated by several studies.[6,9,10] Unfortunately, HPN is associated with complications, including progressive steatohepatitis and further liver failure, catheter-related complications and the inability to cope with the HPN regimen.[11] Intestinal transplantation (ITx) is also an alternative therapy for patients with permanent and irreversible HPN dependence.[12] However, despite its relative safety and efficacy, ITx survival still appears to be lower than with HPN.[6,12–14] Consequently, based on the American Society of Transplantation as well as Medicare and Medicaid, ITx should be considered in patients with permanent HPN dependence and in cases of failure of HPN, high risk of death, severe SBS, frequent hospitalizations and the unwillingness of the patients to accept long-term HPN.[12] Recently, a European study supporting the choice

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of HPN showed that the survival of the patients who fulfilled the criteria for ITx without HPN-related complications was similar to the survival of the patients who did not fulfil the criteria for ITx.[14]

Herein, we report a large series of adult SBS patients over a 25-year period of follow-up to better define these two important clues in the management of SBS patients on HPN: (1) HPN dependence and (2) long-term survival of SBS patients on HPN.

2. Patients and methods

2.1. Patients

From January 1980 to April 2006, all consecutive adult patients with a short bowel syndrome (remnant small bowel length of ≤150 cm) that have required HPN in our institution, an approved centre for IF and HPN, were included in a retrospective cohort study. Patients were recruited from our personal HPN database and/or a standardized hospital inpatient dataset diagnosis. We excluded the patients with evolving primary malignancies present within the first year of the follow-up ($n = 8$), patients who had received treatments other than HPN for intestinal failure, e.g., recombinant human growth hormone or teduglutide and the patients that have discontinued HPN within 3 months ($n = 21$). We included patients who had reconstructive surgery of the remnant small bowel (segmental reversal small bowel was performed in 28 cases). Eighty patients from this series have already been included in a previous study and 30 in the Pironi's study.[6,14] This work has been approved by the local ethical committee according to French law. The data records included the demographic data of the patients, aetiology of SBS, characteristics of past surgical procedures, characteristics of intestinal tract, HPN dependence and patient mortality including the causes of death. The remnant small bowel was evaluated on the basis of operative records and expressed as a length. The remaining colon was evaluated according to the method of Cummings et al.[15] Briefly, the length of the colon was divided into seven sections, each part thus represents 14% of the colon. These divisions correspond approximately to the sites at which jejunocolonic anastomosis were made. The length of remaining colon was expressed as a percentage. SBS was classified as type 1 (jejunostomy), type 2 (jejunocolonic anastomosis), or type 3 (jejuno-ileocolonic anastomosis). Special attention was focused on the presence (or absence) of chronic intestinal obstruction, either functional or mechanical.[16] The routine parameters collected for nutritional evaluation included weight, height, BMI and resting energy expenditure according to the Harris and Benedict equation.[17] Plasma amino acid sampling were performed after a overnight fast, as described previously, in order to determine the post-absorptive plasma citrulline concentration.[18] Post-absorptive plasma citrulline concentration was determined under stable conditions in absence of overt dehydration, early, between 1 and 6 months after SBS constitution and after at least a 2-year adaptive period following re-establishment of digestive continuity.

2.2. HPN management

The conditions under which HPN was administered have been outlined elsewhere.[6,19] The dietary program was composed of unrestricted free solid food ingestion and, especially in patients with end-enterostomy, the use of either oral rehydration solution or mineral Vichy-St-Yorre and tap water restriction. All patients were educated by trained dietetician to promote spontaneous oral hyperphagia. The composition and volume of solutions given to the patients and the number of infusions per week were adjusted to individual needs. The attempt was always made to set up at nutritional balance monitoring as previously described.[6,19] HPN characteristics regarding the composition, volume and frequency of the infusions were collected at the end of the follow-up. The degree of HPN requirement was calculated as the percentage of the daily mean of total parenteral energy infused divided by 1.5 times the resting energy expenditure.[5,20]

2.3. Absorption study

SBS patients underwent a metabolic study to evaluate the intestinal macronutrient absorption at various times during the course of their HPN.[5,20] Briefly, over a 6-day period, the first 3-day equilibrium period was used to confirm that patients were continuing their spontaneous intake of energy, carbohydrates, lipids, proteins, and fibres, while absorption was measured the last 3 days. Unrestricted intake was measured by trained dietetician (food diary) by amount or weight and calculated with Bilnut software (Bourgerette P, Rolshansen M; BILNUT 4.0; SCDA Nutrisoft, Cerelles, France). Stool was collected daily and frozen at −20 °C. Protein, lipid, and total energy were determined by nitrogen elemental analysis (N analyser Flash EA1112; Thermo Scientific, Waltham, MA, the method of Van de Kamer and bomb calorimetry, PARR 1351 bomb calorimeter; Parr Instrument, Moline, IL). Quantification of carbohydrate-derived energy was calculated by subtracting the energy associated with the protein and lipid components from the total energy. The calorie-conversion factors used were 4.2, 9.35, and 5.65 kcal/g for carbohydrates, lipids, and proteins, respectively. The coefficient of net intestinal absorption represented the proportion of ingested energy not recovered in the stool output. The degree of nutritional oral autonomy was calculated as the total calories ingested daily multiplied by the net total caloric absorbed fraction and divided by 1.5 times the resting energy expenditure.[5,20]

2.4. Statistical analysis

All patients were followed-up until death or June 2006 when the data were collected. HPN duration was calculated from the date of HPN start, up to the death, definitive HPN cessation, or end of the follow-up. HPN dependence was defined as unability of patients to be definitively weaned off HPN at the time of data collection. The survival time was calculated from the date of HPN start to the death or end of the follow-up. For statistical analysis of survival, patients who have undergone ITx were presumed dead at the time of the transplantation. HPN dependence and survival probabilities were calculated using the Kaplan–Meier method. HPN dependence and survival variables were compared using univariate and multivariate analyses. HPN dependence and survival distributions were compared using the log rank test, with p values of 0.05 considered statistically significant, according to the concomitant variables of survival and HPN dependence. Qualitative categories of values were defined by dichotomy from median value in two distinct groups of equal size. To identify the independent factors contributing to HPN dependence and survival, Cox proportional hazard models were then adjusted to the above-mentioned variables with an ascending stepwise procedure using SPSS statistical software (SPSS Inc, Chicago, Illinois). Quantitative variables were expressed as medians (ranges) or as means ± standard deviation; both probabilities of survival and Hazard risks (RRs) were provided with 95% confidence intervals (CIs). Spearman's two-tailed test was used to assess correlations. To determine early and postadaptive plasma citrulline concentrations performance, receiver operating characteristic (ROC) curves were constructed and area under curves (AUROCs) calculated with an empirical non parametric method. The charac-

the Wilcoxon test and by Student *t*-test for HPN dependent and independent patients.

3. Results

3.1. Patient's characteristics

(Tables 1 and 2) Two hundred and sixty-eight patients (139 females, median age 52.5 (18–89) years) fulfilled the inclusion criteria. Past history of cancer was noted in 95 (35%) patients (chronic radiation enteritis in 61 cases): gynaecologic carcinoma in 42 cases, digestive carcinoma in 39, urologic carcinoma in 6, Hodgkin's or non-Hodgkin's lymphoma in 4, head and neck carcinoma in 2 and myelodysplastic syndrome in 2. None of these malignancies was active at time of SBS constitution. Median delay between past cancer and SBS constitution was 3.8 (0.3–30.6) years. In one case, a patient with head and neck cancer unrelated to digestive history and arterial mesenteric infarction had a delay between past cancer and SBS constitution less than one year. Median follow-up was 4.4 (0.3–24) years. SBS was classified as type 1 in 48 (18%) cases, type 2 in 179 (67%) and type 3 in 41 (15%) cases. The median length of post-duodenal remnant small bowel was 84 (0–150), and 65 (0–150), and 70 (5–150) cm in type 1, 2, and 3 SBS, respectively (NS). The median percentage of remaining colon was 61 (0–100) %. Twenty eight patients underwent segmental reversal small bowel procedure at time of the re-establishment of digestive continuity (jejunocolonic anastomosis in 27 cases and jejunoileal anastomosis in 1). Chronic intestinal obstruction was noticed in 35 (13%) cases, including mechanical in 29 cases (surgical complications in 9 cases, chronic radiation enteritis in 9, chronic intestinal pseudoobstruction in 6, soft tissue tumour in 5, arterial mesenteric infarction in 3 and volvulus, Crohn's disease and venous mesenteric infarction in 1).

3.2. Nutritional status

At the end of the follow-up, the mean BMI had decreased compared to baseline (20.7 ± 3.9 kg/m^2 vs. 24 ± 4.4 kg/m^2, $p < 0.001$). An adaptive hyperphagia (>1.5 times the resting energy expenditure) was observed in 177 (66%) patients. Oral intake was significantly lower in patients with a chronic intestinal obstruction (1903 kcal/d ± 60 vs. 2327 kcal/d ± 60, $p = 0.01$). Post-absorptive plasma citrulline concentration was 20.8 ± 12.5 and 23.7 ± 12.5 μmol/l, in the early course ($n = 130$) and after at least a 2-year adaptive period ($n = 146$), respectively ($p = 0.07$). The median duration of HPN was 1.7 (0.3–20) years. The mean number of infusions per week was 5.4 ± 1.7 with a volume per infusion of 2449 ± 766 ml and an energy value of 1362 ± 351 kcal per infusion. The mean degree of HPN requirement was 57% ± 25% i.e. HPN represents 57% ± 25% of the total energy expenditure in patients that are still dependent of HPN at the end of the follow-up.

Table 1
Demographic characteristics of *268* adult patients with non-malignant short bowel syndrome.

Characteristics	No of patients (%)
Gender	
Male	129 (*47*)
Female	139 (*53*)
Age at time of short bowel constitution, yrs (SD, range)	
≤ 40 yrs	61 (*23*)
41–59 yrs	124 (*46*)
≥ 60 yrs	83 (*31*)
Causes of bowel resection	
Mesenteric infarction	115 (43)
Arterial/venous	93 (35)/22 (8)
Radiation enteritis	61 (23)
Surgical complications	33 (12)
Volvulus and traumatism	14 (5)
Crohn's disease	15 (6)
Chronic intestinal pseudo-obstruction	11 (4)
Soft tissue tumour	16 (6)
Others	3 (1)

Table 2
Digestive characteristics of *268* adult patients with non-malignant short bowel syndrome.

Characteristics	No of patients (%)
Remnant small bowel	
< 50 cm	87 (*32*)
50–99 cm	95 (*36*)
100–150 cm	86 (*32*)
Digestive circuit anastomosis	
Jejunostomy (type 1)	48 (*18*)
Jejunocolic anastomosis (type 2)	179 (*67*)
Jejunoileocolic anastomosis (type 3)	41 (*15*)
Other digestive features	
Left colostomy	35 (*13*)
Duodenopancreatectomy	5 (*2*)
Segmental reversal small bowel	28 (*10*)

3.3. HPN dependence

One hundred and twenty four (46%) patients were permanently dependent on HPN. Of the 124 patients who were permanent HPN dependent, 17 (14%) were able to discontinue HPN but had to restart definitively HPN after a median delay of 12 (4–123) months. HPN independent patients had a longer remnant small bowel length, greater percentage of remaining colon, and higher plasma citrulline concentration, BMI, oral intake and degree of nutritional oral autonomy ($p < 0,05$) than HPN dependent patients (Table 3). HPN independent patients had respectively a higher and a lower percentage of type 3 and type 1 SBS ($p < 0.001$). Actuarial HPN dependence probabilities were 74%, 64% and 48% at 1, 2 and 5 years, respectively (Fig. 1). In multivariate analysis, HPN dependence was significantly decreased when associated with an early plasma citrulline concentration greater than 20 μmol/l [RR = 0.23 (0.12–0.48), $p < 0.001$], a remaining colon greater than 57% (4/7) [RR = 0.41 (0.26–0.83), $p = 0.001$] and a remnant small bowel length greater than 75 cm [RR = 0.47 (0.26–0.85), $p = 0.001$]. Fig. 2 shows the actuarial HPN dependence probabilities of SBS patients according to the remnant small bowel length and type of anastomosis.

Significant correlations were found between postadaptive plasma citrulline concentrations and the HPN independence ($p = 0.01$), but not with early postoperative plasma citrulline concentrations. To predict the HPN independence, postadaptive plasma citrulline AUROCs were 0.85 (0.78–0.92, $p < 0.001$).

Among the 124 patients that became HPN independent, 54.5% of patients discontinued HPN before 12 months, 19% between 12 and 24 months and 26.5% after 24 months after the re-establishment of digestive continuity. The comparison between the two groups of patients that have been discontinued HPN before ($n = 91$) and after 2 years ($n = 33$) showed that the latest group (after 2 years) was characterized by younger age at SBS constitution (47.1 ± 2.9 yrs vs. 53.6 ± 1.6 yrs, $p = 0.05$).

3.4. Survival, ITx and causes of death

One hundred and five (39%) patients died during the follow-up (Table 4). HPN- and SBS-related complications accounted for 13 (13%) and 14 (13%) deaths, respectively. The main causes of death

Table 3
Comparison of the characteristics of 268 SBS patients according to their HPN status: independent ($n = 144$) or dependent ($n = 124$).

Characteristics of the patients	HPN independent	HPN dependent	*p*
Demographic characteristics			
Female(%)	54	50	0.54
Age at time of SBS constitution (yrs)	52.3 ± 1.3	50.9 ± 1.3	0.48
Initial BMI(kg/m^2)	24.4 ± 0.4	23.6 ± 0.3	0.17
Final BMI(kg/m^2)	21.5 ± 0.4	20.0 ± 0.3[a]	0.002
Causes of SBS (%)			
Mesenteric infarction	39	46	0.27
Arterial	27	42[a]	0.01
Venous	12	4[a]	0.02
Radiation enteritis	26	20	0.17
Surgical complications	18.5	7[a]	0.005
Volvulus and traumatism	6	5	0.79
Crohn's disease	5	6	0.79
Chronic intestinal pseudo-obstruction	1	7[a]	0.01
Soft tissue tumour	4	8	0.30
Remnant bowel			
Small bowel length (cm)	91 ± 3	53 ± 3[a]	<0.001
Large bowel (%)	69 ± 3	51 ± 3[a]	<0.001
Post-absorptive plasma citrulline (μmol/l)			
Postoperative	27.4 ± 1.3	16.5 ± 1.2[a]	<0.001
Postadaptive	29.5 ± 1.4	17.3 ± 1.0[a]	<0.001
Digestive circuit (%)			
Jejunostomy (type 1)	8	26[a]	<0.001
Jejunocolic anastomosis (type 2)	66	67	0.90
Jejunoileocolic anastomosis (type 3)	23	7[a]	<0.001
Other digestive features (%)			
Left colostomy	14	12	0.86
Segmental reversal small bowel	8	12	0.32
Oral intake			
Free oral intake (%)	100	97	0.13
Oral intake (Kcal/d)	2625 ± 68	1964 ± 78[a]	<0.001
Adaptivehyperphagia[a] (%)	75	66	0.14
Oral autonomy degree (%)	90 ± 3	53 ± 3[a]	<0.001
Outcome			
Follow-up (mo)	73 ± 5	71 ± 5	0.79
Survival (%)	78	46[a]	<0.001

[a] Categories statistically significant using chi-2 test and student *t*-test.

in 22 (21%) and second primary malignancy in 18 (17%). There was no significant difference between the causes of death within the first two years compared to the rest of the follow-up. However, trends for a higher rate of death related to an underlying disease in the first two years (28% *vs.* 17%, $p = 0.19$) was observed. The actuarial survival probabilities were 94%, 70%, % and 52% at 1, 5 and 10 years, respectively (Fig. 3). In multivariate analysis, the survival was significantly increased in patients with an age <60 years [RR = 0.65 (0.4–0.97), $p = 0.04$] whereas the survival was significantly decreased in cases with an arterial mesenteric infarction [RR = 3.4 (2.1–5.4), $p < 0.001$], a past cancer history [RR = 2.8 (1.8–4.6), $p < 0.001$] and the presence of an end ostomy [RR = 1.8 (1.2–2.8), $p = 0.006$]. Furthermore, the 10-year survival was significantly higher in patients that became HPN-free compared to those who remained HPN dependent (67.0% ± 0.6% vs. 40.7% ± 0.5%, $p < 0.001$) (Fig. 4).

3.5. Absorption study

The degree of nutritional oral autonomy was available in 224 (84%) patients. Its evaluation was performed 9.0 (0.5–243) months after re-establishment of digestive continuity. The mean degree of nutritional oral autonomy was 69% ± 40% and it was significantly lower in type 1 anastomosis (53% ± 7%) than in type 2 (72% ± 3%) and type 3 (77% ± 7%) anastomosis ($p = 0.02$) although the remnant small bowel length did not differ between each group ($p = 0.29$). The mean degree of nutritional oral autonomy was also lower in patients with chronic intestinal obstruction (52% ± 8% vs. 72% ± 3%, $p = 0.01$). Univariate analysis revealed a degree of nutritional autonomy greater than 70% significantly associated with a higher survival ($p < 0.001$) and a lower HPN dependence ($p < 0.001$) but it was not included in the multivariate analysis because it was evaluated at various time points during the follow-up.

4. Discussion

This study focuses on a cohort of 268 adult SBS patients followed-up over a 25-year period of which a part has been

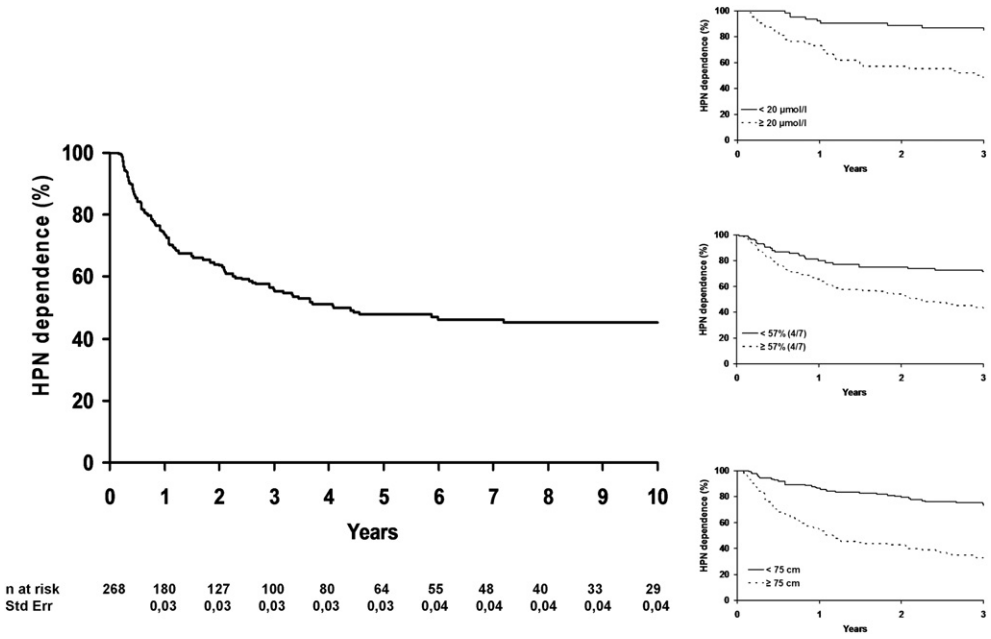

Fig. 1. Actuarial probability of home parenteral nutrition dependence of adult short bowel syndrome patients ($n = 268$), for the overall study population and according to the

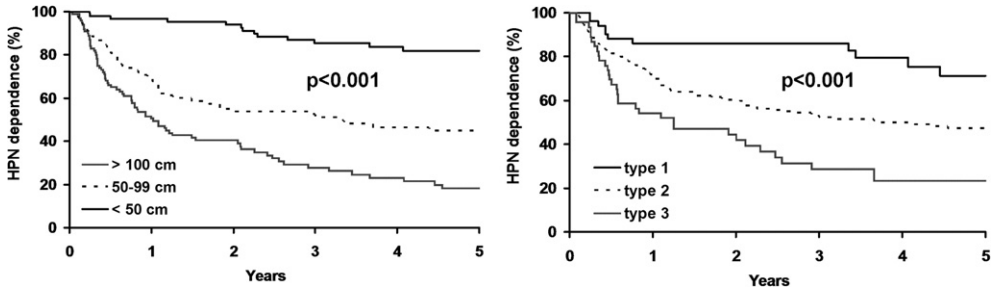

Fig. 2. Actuarial probability of home parenteral nutrition dependence of adult short bowel syndrome patients ($n = 268$), according to the remnant small bowel length and the type of anastomosis.

previously been published.[6] The HPN dependence probability was 47% at 5 years and was significantly associated with a remnant small bowel length greater than 75 cm, a remaining colon greater than 4/7 and a postoperative citrulline concentration greater than 20 μmol/l. These factors should be considered prospectively to guide earlier SBS patients at high risk of permanent HPN dependence on surgical rehabilitation, pharmacological therapy and/or ITx. The survival probabilities were 73% and 56% at 5 and 10 years, respectively. Furthermore, the mortality was mainly associated with underlying diseases and to a lesser extend with SBS- or HPN-related complications, supporting the safety of long-term HPN in approved HPN centres.[16]

We used the same criteria from our previous study, excluding patients with a remnant small bowel length >150 cm and/or evolving primary malignancies.[6] In contrast to the previous study, we also excluded patients that have discontinued HPN within the first 3 months ($n = 21$). Hence, analysis of patients' prognosis and HPN dependence was allowed without interference from confounding variables despite the analysis of numerous variables has inherent bias. Although characterized by lower oral intake, we chose not to exclude chronic intestinal pseudoobstruction- and chronic radiation enteritis-related SBS as well as patients with persistent chronic intestinal obstruction, because we thought they are also representative of the SBS population. Excluding these patients would have also removed patients with chronic peritoneal adhesions, narcotic use and associated extra digestive comorbidity.

Table 4
Causes of deaths in a cohort of *268* adult patients with non-malignant short bowel syndrome.

Characteristics	No of patients (%)
Related to primary disease	22 (*21*)
Radiation enteritis or uropathy	6
Cancer relapse	6
Arterial mesenteric infarction	4
Postsurgical complications	4
Desmoid tumour	2
Related to HPN	13 (*13*)
Sepsis	10
Liver failure	3
Related to short bowel	14 (*13*)
Cachexia	9
Metabolic complication	4
Miscellaneous	56 (*53*)
Cardiovascular disease	21
Secondary primary malignancies[a]	18
Unknown	9
Sepsis	7
HBV recurrence-relatedfulminant hepatitis	1

[a] Second primary malignancies included lung carcinoma in 4 cases, prostatic carcinoma in 2, non-Hodgkin's lymphoma in 2, colorectal carcinoma in 2, urological carcinoma in 2 and leukaemia, head and neck cancer, and small bowel carcinoma in

In this study, We confirmed that the remnant small bowel length has a high predictive value to identified transient or permanent HPN dependence.[6,16] However, the remnant small bowel length cut-off observed here was lower than in our previous study (75 cm vs. 100 cm).[6] The re-establishment of colonic continuity or segmental reversal of the small bowel may have played a role in this decrease.[19,21] We also confirmed that the presence of a significant part (at least 4/7) of remaining colon was a predictor of HPN discontinuation. This observation coincides with previous reports that demonstrate the important role of the colon following massive small bowel resection. This role included the improved absorption of fluid and electrolytes, mucosal hyperplasia, hyperfermentation of malabsorbed carbohydrates attributable to changes in the bacterial microbiota and secretion of enteric hormones involved in the intestinal adaptation (GLP-2, PYY).[5,22–24] Although previous studies have failed to find a significant correlation between the amount of remaining colon and HPN dependence, we demonstrate its benefit in this very large series.[6,20,24,25]

Citrulline is a non essential amino acid produced by the small bowel mucosa. In patients with SBS, the postadaptive plasma citrulline concentration was reported a marker of HPN dependence, under stable conditions and in the absence of renal failure.[18] However, the early assessment of the plasma citrulline concentration has never been evaluated to predict a permanent or transient HPN dependence. In this study, we showed that the early plasma citrulline concentration (evaluated between 1 and 6 months, following the re-establishment of digestive continuity, when oral feeding is fully resumed) was a significant predictor of HPN independence. The role of early plasma citrulline concentration to predict further HPN dependence should be confirmed in a prospective study.

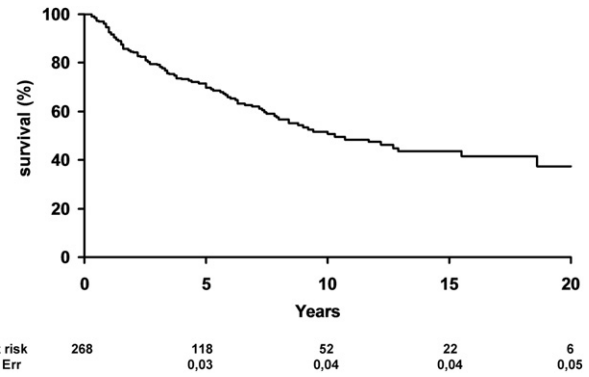

Fig. 3. Actuarial survival probability of adult short bowel syndrome patients on home

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