



Splenectomy in hematology. Current practice and new perspectives

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ABSTRACT

Background and Objective. Progress and changes in the management of blood diseases, in surgery and in videotechnology stimulate a critical reappraisal of splenectomy in hematology.

Design and Methods. We have collected information on the current practice of splenectomy in hematology in Italy and we have reviewed the results of a new technique of laparoscopic splenectomy (LS).

Results. Current splenectomy practice: the current practice in Italy is to offer splenectomy as front-line treatment for hereditary spherocytosis and as second-line for idiopathic thrombocytopenic purpura (ITP) and hemolytic anemia. Splenectomy is also offered in selected cases of leukemia and lymphoma but is going out of practice for hairy cell leukemia and Hodgkin's disease. The number of splenectomies that are performed every year is estimated to be higher than 10 per 10⁶ persons (more than 500 cases per year). Laparoscopic splenectomy (LS): more than 700 cases of LS have been reported so far, for thrombocytopenia (470 cases) as well as for many other hematologic indications. The procedure carries a mortality of 0.8%, and a complication rate of 12%. Time spent in the operating theater ranges from 1.5 to 4 hours, blood transfusion requirement is minimal and the mean post-operative hospital stay is 3 days.

Interpretation and Conclusions. Although a prospective comparison is not available, the results of LS compare favorably with the results of classic open splenectomy, so that LS is likely to become the technique of choice especially when the spleen is small, as in ITP. LS can also have some advantages in other cases of splenectomy, including splenomegaly for leukemia and lymphoma. These data and suggestions should stimulate and renew a discussion about splenectomy in hematology, with the purpose of establishing evidence-based guidelines.

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Key words: splenectomy, laparoscopy, leukemia, lymphoma, anemia, thrombocytopenia

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For many years splenectomy was the main point of contact between hematology and surgery. The indications for splenectomy in hematology are numerous, from diagnostic and staging purposes to splenic rupture due to infarction, from anemia or thrombocytopenia to leukemia or lymphoma. These indications were generated over different historical periods. Many of them are soundly based on common sense and practice, but rarely on evidence. Over time the indications for splenectomy in hematology have undergone some changes,¹ depending on modifications and progress in the management of malignant and non-malignant blood diseases. Major examples are Hodgkin's disease (HD) and hairy cell leukemia (HCL) where new treatment strategies and new therapeutic agents have minimized recourse to splenectomy.²⁻⁵ The use of splenectomy is also influenced by the frequency and the severity of its complications. Late complications mainly involve the immune system and host defence, being infectious, and advise against splenectomy in children.⁶⁻¹⁰ Short term complications are related to the underlying disease and the patient's clinical and hematologic conditions, but also to surgical technique and skill. Progress in surgery has made it possible to perform splenectomy under videolaparoscopic control avoiding laparotomy.¹¹⁻¹⁴ It may, therefore, be opportune to reexamine this meeting point between hematology and surgery and work out evidence-based analysis with the purpose of reaching a consensus and proposing guidelines. This review is propedeutic to the analysis and stimulatory to the discussion, reporting on the splenectomy policies that are currently practiced in Italy and illustrating the technique and the results of videolaparoscopic splenectomy. Data and discussion are limited to splenectomy in adults.

Splenectomy practice in Italy: an overview

To collect information on the current practice of splenectomy in hematology in adults, we addressed a simple questionnaire to 52 centers of which 41 were Divisions of Hematology and 11 were Divisions of Internal Medicine or Oncology with a known interest in hematology. Centers were located at University or General Hospitals all over Italy. Forty-seven answers (90%) were received. The questionnaire asked the

respondents to identify the current main indications for and contraindications to splenectomy in chronic idiopathic thrombocytopenic purpura (ITP), hemolytic anemia, primary myelofibrosis (MF), non-Hodgkin's lymphomas (NHL), chronic lymphocytic leukemia (CLL), HCL and HD. In all the answers, a distinction was made between hereditary spherocytosis (HS) and chronic autoimmune hemolytic anemia (AHA). Moreover, the answers clarified whether, in any given condition, splenectomy was recommended always, sometimes, never or exceptionally.

All 47 Institutions declared using splenectomy in HS, AHA and chronic ITP (Table 1). In HS all centers but two advise splenectomy as front-line treatment without any major contraindications. In chronic AHA and in chronic ITP splenectomy is mainly advised in case of resistance to treatment or when the course is heavily dependent on chronic treatment. Major contraindications, as identified by responding centers, are advanced age (42% of responding centers for AHA, 60% for ITP), cold IgM autoantibodies (9%), HBV or HCV positivity (7%), immunodeficiency or HIV positivity (4%) and systemic autoimmunity (9%).

In primary MF with liver/spleen myeloid metaplasia (Table 1), splenectomy is no longer recommended in 13/47 centers (28%). Major indications are splenomegaly (68%), anemia (21%) and symptoms (47%). Major contraindications are advanced age (42% of responding centers), a high platelet count (39%) and disease acceleration or progression (27%). Splenectomy for NHL, CLL and HCL (Table 1) is currently not practised by 2%, 28% and 51% of the centers, respectively. Major indications are splenomegaly (41%, 42% and 21%), primary splenic lymphoma or isolated splenomegaly (67% in NHL), and residual or refractory splenomegaly (20%, 28% and 30%).

In HD, splenectomy is out-of-practice in 32/47 centers (68%) (Table 1). In the remaining 15 centers splenectomy is practised only for the surgical staging of a few, selected early stage cases and sometimes also for the management of an isolated splenomegaly.

To summarize, splenectomy is currently indicated as front-line treatment in HS, irrespective of the degree of anemia, because only two of the 47 centers answered that the recommendation for splenectomy depended on Hb level. It is recommended as second-line treatment in chronic AHA and chronic ITP, when medical treatment fails or treatment duration and toxicity are not acceptable. Interestingly, disease severity and duration were not indicated, while five centers pointed out that splenectomy can be required to eliminate or reduce the anxiety of living with ITP or AHA. In MF, in lymphomas and in chronic lymphoproliferative disorders splenectomy is no longer used as front-line treatment. However, it is still recommended in MF when splenomegaly is massive and symptomatic, and in NHL and CLL, mainly when spleen volume is large or the spleen is refractory to treatment, with anemia or thrombocytopenia. The case is different with

HCL, where 50% of the institutions have abandoned splenectomy completely, due to the increasing availability of very effective medical treatments⁴ and with HD, where staging laparotomy and splenectomy have fallen out of use, either because of the improvement in imaging techniques or because of the increased effectiveness of other treatments.^{2,3,15} Fear that splenectomy can increase the rate of late second tumors¹⁶⁻¹⁸ may also have contributed to the abandoning of splenectomy.

Laparoscopic splenectomy

Splenectomy was traditionally performed through a midline or left subcostal laparotomy (open splenectomy, or OS). The development of new video-technology combined with advances in surgical instrumentation has allowed the surgeon to enter the peritoneum through multiple tiny incisions of the skin under direct visualization offered by a fiber-optic scope and a videocamera connected to a TV screen. This new laparoscopic technique allows several surgical procedures to be performed, for example cholecystectomy, appendectomy, hernia repair, gastric fundoplication, adrenalectomy.¹⁹ In 1992, Carroll *et al.* in Los Angeles were the first to use laparoscopy for splenectomy.¹¹ Since then, several centers worldwide have adopted this new approach. The abdomen is insufflated with CO₂ to create a virtual chamber in the peritoneal sac. Special hollow devices, called trocars, are used to introduce the fiber-optic scope and the laparoscopic instruments into the peritoneal cavity. The operation can now be performed entirely laparoscopically. Usually 4 to 5 trocars, located in the upper abdomen, are enough to perform a laparoscopic splenectomy (LS). The operation starts with dissec-

Table 1. A summary of the major indications for splenectomy, based on current practice in 47 Italian hematologic centers.

	Chronic							
	HS %	AHA %	ITP %	MF %	NHL %	CLL %	HCL %	HD %
Always	95	0	0	0	0	0	0	0
Sometimes	5	100	100	72	98	72	49	32
Never or exceptionally	0	0	0	28	2	28	51	68
Resistance to treatment	-	95	79	2	0	8	30	0
Treatment dependence	-	6	23	0	0	0	0	0
Bleeding	0	0	17	0	0	0	0	0
Severe thrombocytopenia	0	2	30	8	15	15	4	0
Severe anemia	5	0	0	21	15	19	2	0
Spleen volume	0	0	0	68	41	42	21	0
Residual or refractory splenomegaly	-	-	-	0	20	28	30	0
Isolated splenomegaly	-	-	-	-	67	2	0	4
Symptoms	0	0	0	47	6	4	2	0
Pathologic staging	-	-	-	-	2	-	-	30

tion of the spleno-colic ligament at the lower pole of the spleen. Mobilization of the spleen proceeds upward by dissection of the spleno-renal ligament and of the spleno-phrenic attachments at the upper pole of the spleen. The splenic vein and artery are now best managed with the aid of a mechanical linear stapler loaded with vascular cartridges. When the spleen is completely free in the abdominal cavity, it can be retrieved either by morcellation into a strong plastic bag or full-size through enlargement of a trocar incision or through an accessory suprapubic incision, when pathologic examination of the whole organ is required. The use of a fiber-optic scope connected to a TV screen allows the surgeon to perform the entire procedure under direct vision. Moreover video-technology instrumentation permits magnification of the anatomic structures. Liver, abdominal and retroperitoneal lymph nodes, accessory spleens and pelvic structures can also be well visualized during the laparoscopic procedure. A careful abdominal exploration with multiple biopsies can be performed allowing complete disease staging when necessary.

LS is a technically demanding procedure and surgeons follow a well-defined learning curve. The experience of the surgical team is the main determinant of the duration of surgery. The reported operating theater time ranges between 1.5 and 4 hours.^{13,20-32} Other important factors are spleen volume, the presence of an accessory spleen and obesity. LS for HD clearly requires a longer time because of the staging procedure. The accuracy of LS for staging is difficult to evaluate. However, based on our experience of 15 cases of LS and 40 cases of OS³² there is no suggestion that LS is less accurate than OS and we think that the magnified view provided by the laparoscope can even improve the detection of small foci of the disease. For the same reason, LS is comparable to OS for the detection of small accessory spleens. This is particularly important in chronic ITP, where failure to recognize and remove an accessory spleen can be responsible for the persistence of thrombocytopenia.¹⁰ With LS accessory spleens are found in 5 to 25% of cases, and the same frequency is reported with OS.^{12,23-24,26-28,31,33-34}

Intraoperative blood loss ranges from less than 50 mL up to 500 mL, but in some cases a blood loss of more than 1000 mL has been reported, requiring conversion to laparotomy. However, conversion may also be recommended depending on the rapidity of the blood loss and on the patient's age and general conditions.

The post-operative course after LS averages less than 4 days, with 50% of patients being advanced to oral diet the day after surgery.^{13,20-40} The duration of the post-operative stay is obviously related to the frequency and severity of post-operative complications. These are shown in Table 2, based on 500 reported cases with available information.^{13, 20-40} Major (6%) and minor (6%) complications were reported in 60 of 500 cases or 12% overall. There were four deaths;

Table 2. Mortality and morbidity of laparoscopic splenectomy in 500 reported cases. Four patients died because of: CNS bleeding due to persistent severe thrombocytopenia (2 cases), complications related to cytotoxic treatment for NHL (1 case), myocardial infarction (1 case). Complications were seen in 60 cases (12%), and were reported to be major in 30 cases (6%).

Deaths	4	0.8%
Major complications		
- pleuropulmonary	12	2.4%
- deep venous thrombosis	5	1.0%
- bleeding	5	1.0%
- subphrenic hematoma or abscess	4	0.8%
- herniation at trocar site	2	0.4%
- diaphragmatic perforation	1	0.2%
- transitory ischemic attack	1	0.2%
Total	30	6.0%
Minor complications*	30	6.0%

*Including wound infection (0.8%), transient serum amylase elevation (0.6%), back pain, hematuria from Foley catheter, subcutaneous emphysema, prolonged ileus, atrial fibrillation, transient pericardial effusion, pain at trocar site, urinary retention, scrotal edema and paresthesia.

two due to hemorrhage associated with persistent severe thrombocytopenia,²⁶ one to cytotoxic treatment,²⁶ and one to myocardial infarction.²² It is worth noting the low frequency of pleuropulmonary and pleuric complications (2.4% and 1%, with one case of diaphragmatic perforation).

Not all the complications and the problems that can occur during LS can be managed laparoscopically. In some cases, laparotomy is required and LS is converted to OS. The reported conversion rate for hematologic diseases ranges from none to 18%,^{13,20-40} depending on the experience of the surgical team and on the degree of splenomegaly, which is associated with more extensive adhesions and particularly with hemorrhage from the splenic vein or artery at the hilum or with bleeding from the parenchyma or short gastric vessels. Extensive bleeding is by far the commonest cause of conversion. A loss of more than 1000 mL of blood demands immediate conversion in any case.

The operative costs, including instrumentation, operating theater, hospitalization and treatment of complications, have been estimated to range between 7,000 and 18,000 US dollars for LS vs 9,000 to 14,000 US dollars for OS.^{25-28, 31}

There are no studies prospectively comparing the results of OS and LS and it is difficult that such studies will be ever done. However, in several reports,^{22-28, 31-32} an attempt was made to provide the data of LS together with data from prior OS, so as to make a comparison possible. These data are summarized in Table 3, and they help to form a clear and consistent picture of LS. The operating theater time used for LS is distinctly longer than that for OS (median 196 vs 121 minutes), the estimated blood loss is similar, the frequency of the detection of an accessory spleen is

Table 3. A summary of nine reports comparing laparoscopic splenectomy (LS) with open splenectomy (OS). All the cases reported by Schlinkert *et al.*²³ and Watson *et al.*³¹ and about 50% of all the other cases concerned treatment of ITP, with the exception of the report by Bacarani *et al.*³² that concerned HD. The differences (asterisk, *p*-value < 0.05) were calculated in the original reports. NR = not reported.

References	Number of cases		Incidence of accessory spleen (%)		Mean operating theater time (min)		Mean estimated blood loss (mL)		Mean time to liquids (days)		Mean post-operative stay (days)		Complications %		Mortality %		
	LS	OS	LS	OS	LS	OS	LS	OS	LS	OS	LS	OS	LS	OS	LS	OS	
Rhodes 1995	24	11	NR	NR	120*	75*	NR	NR	NR	NR	3.0*	7.0*	8	27	4	0	
Schlinkert 1995	7	14	0	14	154*	68*	NR	NR	0.7*	2.6*	2.1*	5.0*	0	21	0	0	
Brunt 1996	26	20	11	5	202*	134*	222	376	1.4*	4.1*	2.5*	5.8*	23	30	0	0	
Smith 1996	10	10	NR	NR	261*	131*	NR	NR	1.9*	4.4*	3.0*	5.8*	0	20	0	0	
Watson 1997	13	47	15	6	88	87	NR	NR	NR	NR	2.1*	13.4*	0	19	0	0	
Diaz 1997	15	15	20	20	196*	116*	385	359	NR	NR	2.3*	8.8*	7	13	0	0	
Friedman 1997	63	74	17	13	153	121	259	437	1.5*	3.2*	3.5*	6.7*	4	17	0	3	
Glasgow 1998	52	28	13	25	196*	156*	274	320	2.0*	4.3*	4.8*	6.7*	10	14	6	0	
Baccarani 1998	15	40	NR	NR	202*	144*	NR	NR	1.9*	3.2*	4.4*	6.7*	6	28	0	0	
Total	225	259														1.5	0.7
Median			13	13	196	121	266	367	1.7	3.6	3.0	6.7	6	20	-	-	

**p*-value < 0.05.

similar, the *time-to-liquids* and the post-operative stay are significantly shorter, and complications are likely to be less frequent. Mortality is low with both operations.

The indications for LS are not yet defined. Several hundred cases have been reported so far (Table 4) with the great majority having been carried out in chronic ITP, reflecting the frequency of the disease, the large consensus on splenectomy¹⁰ and the small volume of the spleen, hence the convenience of LS, where bleeding can be controlled as carefully as with OS and the post-operative course is short and uncomplicated. LS has also been performed for several other hematologic indications (Table 4), including leukemia and lymphoma. A recent study by Decker *et*

*al.*⁴⁰ emphasized the feasibility and safety of LS for blood malignancies reporting that post-operative morbidity and mortality were not greater than in patients who were operated on for anemia or thrombocytopenia, although the time spent in the operating theater was longer, conversion to OS was more frequent, and more blood transfusions were required. Probably, the major problem is the volume of the spleen; a huge splenomegaly implies older disease with more clinical problems, more adhesions, more bleeding and more technical difficulties. Table 5 shows the data of 48 cases of LS that were performed in Udine, divided according to the degree of splenomegaly.⁴¹ There were 14 cases of splenomegaly, including NHL (8 cases), CLL (1 case), MF (2 cases) and HS (3 cases), with a median spleen weight of more than 2000 g. The main difference with the 34 cases of LS with no splenomegaly (i.e. with a spleen weight of less than 500 g) concerned the operating theater time (168 vs 115 min), blood loss (504 vs 226 mL), blood transfusions, that were required in 5 of 14 cases of splenomegaly but in none of the 34 cases without splenomegaly, and the time to oral diet (1 vs. 2 days). The rate of conversion to OS (7% and 3%), post-operative complications (7% and 6%) and post-operative hospital stay (5 and 4 days) were similar.

Conclusions

LS is likely to be the intervention of choice when splenectomy is indicated in a patient with a small spleen and with uncomplicated disease. The prototype disease is chronic ITP, in which it has been shown that thrombocytopenia does not cause any particular or unexpected difficulty. For other indications and in any case of massive splenomegaly the difficulties that are encountered with LS are the same as those with OS. The mortality and the frequency of the complica-

Table 4. Hematologic indications for laparoscopic splenectomy: literature data.

	No. of cases
Chronic idiopathic thrombocytopenic purpura	437
HIV related thrombocytopenia	33
Hereditary spherocytosis	63
Hodgkin's disease (staging)	59
Chronic autoimmune hemolytic anemia	56
Non-Hodgkin's lymphoma	29
Chronic lymphocytic leukemia	16
Myeloproliferative disorders, including myelofibrosis	11
Hairy cell leukemia	8
Sickle cell disease	4
β thalassemia	2
TOTAL	718

Table 5. Comparison of laparoscopic splenectomy for normal sized spleen (spleen weight less than 500 g) and for splenomegaly (spleen weight more than 500 g). All the patients were operated on at the Department of Surgery, Udine University.⁴¹ Values are mean \pm SD.

	Spleno- megaly (> 500 g)	Normal sized spleen (< 500 g)
No. of cases	14	34
Spleen weight (g)	2350 \pm 1311	167 \pm 86
Conversion to open splenectomy	1 (7%)	1 (3%)
Operation theater time (minutes)	168 \pm 67	115 \pm 53
Intra-operative estimated blood loss (mL)	504 \pm 352	226 \pm 220
Blood transfusions		
no. of cases requiring blood transfusion	5 (36%)	0
mean number of units per patient	2.6	-
Clear to oral diet (days)	2.0 \pm 1.0	1.0 \pm 0.5
Post-operative complications	1 (7%)	2 (6%)
Post-operative hospital stay (days)	5 \pm 2	4 \pm 2

tions are likely to be identical, depending on disease, patient, specific surgical experience, and medical care before and after the operation. Currently, we practice LS in all cases, bearing in mind that a conversion to OS can be decided and performed whenever required in the operating theater. In other institutions the practice is different. The questionnaire that was sent to the hematologic centres included a question concerning the operative technique. Only one center answered that all the operations were LS, while in 28 centers (59%) all the splenectomies are still performed according to the classic open technique. In the remaining 17 centers (37%) both techniques, OS and LS, are in use and in these centers the major contraindications to the laparoscopic technique were reported to be spleen volume (82% of centers), low platelet count (41%), staging (41%) and advanced age (18%). MF (53%), CLL (35%) and NHL (35%) were also indicated as contraindications to LS. We do not share this opinion, but clearly more experience must be gained and more evidence provided, before LS gains a larger consensus. Finally, it is also interesting and important to have an estimate of the size of the demand. Our questionnaire asked the centers to provide an estimate of the numbers of splenectomies that are expected to be done yearly. The total ranges from 175 to 210 for chronic ITP, from 86 to 113 for NHL, from 54 to 89 for HS and chronic AHA, from 40 to 50 for CLL, from 30 to 60 for MF, from 21 to 28 for HD and from 13 to 19 for HCL. Overall, about 500 splenectomies (range 419 to 568) are performed yearly in the responding centers. This is obviously an underestimate of all the splenectomies that are performed in Italy, because the questionnaires were sent only to hematologic centers, and five did not respond. Therefore, over 500 splenec-

tomies per year, or approximately 10 splenectomies per 10⁶ persons per year are likely to be done in Italy for hematologic indications. We think that a consensus on indications and techniques is worth developing, also taking into account the progress in the management of HD^{2,3,15-18} and HCL,⁴ the uncertainties in the treatment of chronic ITP,^{10,42} and the recent analysis of splenectomy and risk of blastic transformation in MF.⁴³ It may be difficult to reach a consensus and to propose guidelines based only on retrospective reviews and on the confrontation of individual opinions and institutional practices. The establishment of a prospective splenectomy registry covering a 2 or 3-year period would probably be more appropriate.

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UB collected and analyzed the data and wrote the report, which was critically reviewed by all the other authors. GT and AD were responsible for the surgical program and data. FZ was responsible for medical program and data. The authors are listed in an order reflecting their individual contribution to the study. FB and MB were responsible for the study, reviewed the manuscript, and are listed as last co-authors.

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