Review

Splenectomy in Myelofibrosis: Indications, Efficacy, and Complications

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Abstract

Splenomegaly, which may range from a few centimeters below the left costal border to massive dimensions, is one of the most characteristic features in patients with advanced myelofibrosis (MF). Splenectomy may offer an effective therapeutic option for treating massive splenomegaly in patients with MF, and especially in cases of disease refractory to conventional drugs, but it is associated with a number of complications as well as substantial morbidity and mortality. Whether splenectomy should be performed before allogeneic hematopoietic stem-cell transplantation is also controversial, and there is a lack of prospective randomized clinical trials that assess the role of splenectomy before hematopoietic stem-cell transplantation in patients with MF. Although splenectomy is not routinely performed before transplantation, it may be appropriate in patients with massive splenomegaly and related symptoms, so long as the higher risk of graft failure in such cases is taken into account. This review aims to describe the efficacy, indications, and complications of splenectomy in patients with MF; and to evaluate the long-term impact of splenectomy on patient survival and risk of disease transformation.

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Introduction

Patients with myeloproliferative neoplasms (MPNs) often present with splenomegaly, which is one of the most characteristic features in patients with advanced myelofibrosis (MF).[1] Splenomegaly, which is caused by extramedullary hematopoiesis (also known as myeloid metaplasia), may range from a few centimeters below the left costal margin to massive dimensions, and it is linked to debilitating symptoms and complications such as abdominal pain, difficulty bending and walking, augmented satiety, weight loss, cytopenias, portal hypertension, and splenic infarction.[1,2]

Extramedullary hematopoiesis is not limited to splenic involvement but can also affect other sites, such as the liver (and, as a consequence, hepatomegaly and alterations of the liver function) and, less frequently, the lung, kidney, central nervous system, lymph nodes, and skin or soft tissues.[2] Splenectomy is an effective treatment for massive splenomegaly in patients with MPNs, but it is associated with a number of complications, as well as substantial morbidity and mortality.[1]

Whether splenectomy should be performed before allogeneic hematopoietic stem-cell transplantation (HSCT) is controversial, given the morbidity and mortality of splenectomy compared to the faster hematologic recovery after transplantation. Although splenectomy is not routinely performed as preparation for HSCT, this procedure may be more likely to be performed in patients with massive splenomegaly because of their higher risk of graft failure.[3] Splenic irradiation may also be used to reduce the spleen size and related symptoms; however, its use is quite limited, and the benefit is still debatable.

The advent of Janus kinase (JAK) 1/2 inhibitors, which decrease splenomegaly and relieve MF-related symptoms, has had a major

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impact on the management of splenomegaly and has removed some indications for splenectomy. However, a significant portion of patients have disease that does not respond to JAK inhibitors, or splenic response is lost after being obtained.

This review aims to describe the efficacy, indications, and complications of splenectomy in patients with MF; and to evaluate the long-term impact of splenectomy on patient survival and risk of transformation to acute myeloid leukemia.

Role of Splenectomy in Treatment of MF

Splenectomy is often used to treat symptomatic splenomegaly, which is refractory to drug therapy. Indications for splenectomy in MF include abdominal pain and discomfort, symptomatic portal hypertension, severe thrombocytopenia, and frequent red blood cell transfusions.[4] The effectiveness of splenectomy has been described in a number of studies, with outcomes highlighting improvements in anemia, thrombocytopenia, and portal hypertension as well as the elimination of splenomegaly-related symptoms.[1,4-6] However, splenectomy in patients with MF may also be associated with numerous complications (eg, reactive thrombocytosis in the postoperative period, thrombohemorrhagic phenomena), substantial operative morbidity and mortality, and disease transformation.

A high incidence of perioperative mortality (9%) and morbidity (31%) was described in 223 patients with MF with myeloid metaplasia who underwent splenectomy as a therapeutic intervention.[4] In these patients, the primary indications for surgery were transfusion-dependent anemia (45.3%), symptomatic splenomegaly (39.0%), portal hypertension (10.8%), and severe thrombocytopenia (4.9%). Among the 203 patients who survived surgery, median postsplenectomy survival time was 27 months (range, 0-155 months), and the incidence of blast transformation was 16.3%. Notably, increased spleen mass and preoperative thrombocytopenia increased the risk of blast transformation.

In a retrospective review of 26 patients with MF and myeloid metaplasia who underwent an open splenectomy between 1979 and 1995 at the Boston University Medical Center, the main indications for splenectomy were progressive transfusion-dependent anemia (n = 11), painful splenomegaly (n = 10), and hypercatabolic symptoms associated with cytopenias (ie, weight loss, fever, and fatigue) (n = 5).[7] The median overall survival was 28 months from the time of splenectomy, and 3 patients died as a result of sepsis associated with a cardiac event within 1 month of surgery; two thirds of patients experienced complications, with thrombocytosis being the most common event occurring > 1 month after splenectomy (31%).

Although associated with substantial risk, splenectomy may be considered in patients with MF with symptomatic splenomegaly refractory to conventional treatment as well as those with severe constitutional symptoms, transfusion-dependent anemia, or portal hypertension resulting from the increased portal flow.[2,4] In the era of JAK1/2 inhibitors, the indication to splenectomy in MF patients can be limited to patients with disease that is unresponsive to JAK inhibitors. However, it must be highlighted that few data are available on the efficacy of splenectomy in patients treated with JAK inhibitors (ie, ruxolitinib).

Radiotherapy as an Alternative to Splenectomy

As an alternative to splenectomy, splenic irradiation is a noninvasive treatment option used to reduce spleen size and provide palliative relief of splenomegaly symptoms in patients with MPNs. The total dose of radiation ranges from 0.15 to 65 Gy per course, with its administration fractionated (ie, spread out over time).[2] Radiotherapy may be indicated in patients who are not eligible for surgery and for the palliative relief of pain associated with splenic infarction; however, its effect is generally not lasting, and there is an increased risk of severe and sustained cytopenias, with higher rates of infection and bleeding.[8-10]

Splenic irradiation (daily fractions of 0.4-1 Gy) was effective for the palliation of symptoms related to treatment-refractory MF in 15 patients with one or more of the following: constitutional symptoms, splenic pain, enlarged spleen, and anemia requiring > 2 units of red blood cell transfusion per month.[8] Patients received a median dose of radiotherapy of 9.8 Gy (range, 0.6-30.5 Gy) per treatment over a median duration of 22 days. In total, the disease of 9 patients (60%) responded to treatment, with a median duration of 10 months (range, 1-19 months). However, response to splenic irradiation was found to be variable; it was more effective on constitutional symptoms, splenic pain, and spleen size.

Transient palliation of symptomatic splenomegaly was achieved with splenic irradiation as shown by a retrospective analysis of 14 patients with primary MF.[11] Overall, 13 (93%) of 14 patients had a reduction in spleen size, which persisted for a median of 2.2 months (range, 0.1-13.8 months), while symptom relief, which occurred in 12 (86%) of 14 patients, lasted for a median of 2.5 months (range, 0.1-16.5 months). Median survival after splenic irradiation was 18.5 months (range, 0.1-71.9 months). Overall, this study showed that despite having a high rate of palliation in patients with symptomatic splenomegaly, symptom relief and reductions in spleen size after splenic irradiation were transient.

It is much more difficult to evaluate the role of pretransplantation splenic irradiation in patients with MF. Long-term follow-up of splenic irradiation before HSCT for chronic myeloid leukemia in 225 patients (112 with and 113 without splenic irradiation) found no significant differences in terms of overall survival, nonrelapse mortality, relapse incident, and relapse-free survival at both 15 and 25 years.[12] Hence, splenic irradiation before HSCT did not increase relapse incidence or transplant-related mortality.

The role of splenic irradiation before HSCT in MF patients is not well established and has been investigated in only a few small studies.[13,14] Nonetheless, low-dose splenic irradiation was found to significantly reduce spleen size (median decrease 10 cm, 36%), and was a safe and well-tolerated adjunct to HSCT in 8 hypersplenic patients with MF.[13]

In a more recent study, Helbig et al[15] assessed the outcome of pretransplantation splenic irradiation in 44 patients with MF who underwent allogeneic HSCT. Compared to nonirradiated patients, no beneficial effects on posttransplantation outcomes were identified for irradiated patients, and the authors concluded that splenic irradiation should not be routinely recommended.

Low-dose splenic irradiation to decrease splenomegaly before HSCT with a reduced-intensity conditioning regimen may be safe,

according to published case reports of two elderly patients with MF.[16] Splenic irradiation (4 Gy) gradually decreased massive splenomegaly and resolved MF-related symptoms; neither patient experienced engraftment failure, and complete remission was achieved.

Efficacy of Splenectomy, Its Complications, and Impact on Survival and Transformation

The most frequent indications for splenectomy in patients with MF, according to reported case series, are progressive and symptomatic splenomegaly, uncontrolled anemia and thrombocytopenia, and portal hypertension due to massive splenomegaly. Therefore, the goal of splenectomy should be to better control anemia and thrombocytopenia, and to improve portal hypertension symptoms.

Table 1 summarizes the published experiences on postsplenectomy outcomes and presplenectomy risk factors. Complications after splenectomy should be divided into perioperative and long term. Among perioperative complications, which are observed in approximately 30% of cases, the most frequent are bleeding (14%) thrombosis (13%), and infections (9%). These complications are fatal in approximately 8% of splenectomized patients, with infection and bleeding representing the most frequent causes of mortality.

The largest experience was conducted at the Mayo Clinic; it retrospectively analyzed 314 MF patients who had undergone splenectomy over a 3-decade period (1976-2004).[5] This analysis showed a decrease in perioperative thrombohemorrhagic complications during the last decade analyzed. It is possible that the use of platelet-lowering therapy, which was provided to 53 patients, played

Table 1 Postsplenectomy Outcomes in Patients With Myeloproliferative Neoplasms

Characteristic	Barosi 1998[17] (N = 87)	Tefferi 2000[4] (N = 223)	Mesa 2006[5] (N = 314)	Santos 2014[1] (N = 50)	Tefferi 2017[18] (N = 120)
Perioperative					
Complications	NR	68 (30.5)	87 (27.7)	NR	NR
Bleeding	NR	33 (14.8)	44 (14)	NR	NR
Thrombosis	NR	16 (7.2)	31 (9.9)	8 (16)	34 (28)
Infection	NR	19 (8.5)	31 (9.9)	NR	NR
Fatal complications					
Complications	NR	20 (8.9)	21 (6.7)	NR	NR
Infection	NR	6 (2.7)	8 (2.6)	NR	NR
Bleeding	NR	10 (4.5)	7 (2.2)	NR	NR
Thrombosis	NR	3 (1.3)	2 (0.6)	NR	NR
Other	NR	-	5 (1.6)	NR	NR
Postsplenectomy outcomes					
Leukemic transformation	23 (26.4)	1 (0.4)	45 (14.3)	9 (18)	30 (25)
Accelerated hepatomegaly	NR	NR	32 (10.2)	NR	NR
Postsplenectomy improvements					
Splenomegaly-related symptoms	NR	NR	121/158 (48.8)	NR	NR
Constitutional symptoms	NR	136 (67)	NR	NR	57/67 (85)
Anemia	NR	76 (37.6)	39/78 (50.0)	21/45 (47)	40/68 (58.8)
Thrombocytopenia	NR	NR	NR	NR	43/43 (100)
Severe thrombocytopenia	NR	0	10/33 (30.3)	NR	NR
Portal hypertension	NR	101 (50)	19/47 (40.4)	NR	NR
Postsplenectomy survival					
Median (range) months	NR	27 (0-155)	19 (14-22)	20% at 5 years	18
Presplenectomy risk factors	• Plt $< 100 \times 10^9$/L • PB blasts	• Plt $< 50 \times 10^9$/L • Hypocellular BM	• Plt $< 100 \times 10^9$/L	• NR	• Plt $< 50 \times 10^9$/L • PB blast $> 5\%$ • Age > 60 years • WBC $> 25 \times 10^9$/L

Data are presented as n (%) unless otherwise indicated.
Abbreviations: BM = bone marrow; NR = not reported; PB = peripheral blood; Plt = platelet count; WBC = white blood cell count.

at least a partial role in avoiding thrombohemorrhagic complications—that is, in 40 (75.5%) of 53 patients with postsplenectomy thrombocytosis who received medical platelet reduction, and in 11 (84.6%) of 13 patients who underwent platelet apheresis.[5] However, these suggested benefits of platelet-lowering therapy are only hypothetical; a protective role should be proven only by a randomized, interventional clinical trial.

Postsplenectomy survival was 19 months (95% confidence interval, 14-22) and appears to be inversely related to preoperative thrombocytopenia (platelet count $< 100 \times 10^9$/L). Improvement of anemia was seen in 50% of patients, 48.8% of patients experienced a reduction in symptoms, and 40.4% of patients had an improvement in signs of portal hypertension. Platelet count improved in 30.3% of patients who were referred to splenectomy for severe thrombocytopenia.[5]

In a later series, Tefferi et al[18] analyzed 120 consecutive patients with MF who underwent splenectomy between 2001 and 2016 at the same institution and designed a Mayo Clinic prognostic model for postsplenectomy survival. In this retrospective analysis, the indication for splenectomy included symptomatic and progressive splenomegaly that was refractory to drug therapy, the need for frequent red blood cell transfusions, and symptoms related to portal hypertension such as ascites, edema, and recurrent gastrointestinal bleeding.

After a median follow-up of 1.3 years, 79% of patients died, 28% experienced thrombotic events, and leukemic transformations were recorded in 25% of patients.[18] Overall, 58% of patients experienced a hematologic response consisting of transfusion independency (26%) or a reduction in transfusion need (32%). An increase in platelet count after splenectomy was found in all 43 patients with platelet count $< 50 \times 10^9$/L at the time of splenectomy.[18] Multivariable analysis identified 4 risk factors associated with shortened postsplenectomy survival: age > 65 years, leukocyte count $> 25 \times 10^9$/L, circulating blasts $\geq 5\%$, and the need for red blood cell transfusion before splenectomy. Starting from this finding, a risk model for postsplenectomy survival in MF was generated, which identified 3 categories: high (3-4 risk factors), intermediate (2 risk factors), and low (0-1 risk factors). Three-year and median postsplenectomy survival were 47% and 2.9 years for low-risk patients (n = 64), 11% and 1.3 years for intermediate-risk patients (n = 38), and 0 and 0.3 years for high-risk patients, respectively.[18] Ideally, this prognostic tool could help identify MF patients who can benefit most from splenectomy.

A further retrospective analysis on the same cohort of 120 MF patients assessed the impact of a preemptive full therapeutic dose or low-dose systemic heparinization, initiated within 1 week of surgery as long as hemostasis was secured, in reducing the risk of early thrombotic events after splenectomy in MF patients.[19] The decision to use proactive systemic anticoagulation was based on the treating physician's choice, and only major arterial or venous thrombotic events occurring within the first 2 months after splenectomy were analyzed. Of the 17 patients who received full systemic heparinization, none experienced postsplenectomy thrombosis, whereas this complication occurred in 15 (26%) of 58 patients receiving low systemic heparinization and in 17 (40%) of 43 patients who received no systemic anticoagulation ($P = .002$). Major hemorrhagic events before or after the initiation of anticoagulant therapy were similar among the 3 groups. This study suggests that treatment with full therapeutic dose heparin therapy is more effective in preventing early thrombotic complications after splenectomy for MF. Of note, the occurrence of early thrombotic events after splenectomy did not affect postsplenectomy survival or leukemia-free survival.

As previously mentioned, the incidence of perioperative mortality and morbidity were 9% and 31% among 223 MF patients who underwent splenectomy as a therapeutic intervention at the Mayo Clinic.[4] The median postsplenectomy survival was 27 months, and platelet count $< 100 \times 10^9$/L and hypocellular bone marrow were identified as independent preoperative risk factors associated with reduced survival. A durable response in constitutional symptoms, portal hypertension, and transfusion-dependent anemia were observed in 67%, 50%, and 23% of patients, respectively, while none experienced stable improvement of severe thrombocytopenia. Complications after splenectomy included progressive hepatomegaly (16.1%) and thrombocytosis (22%), leading to an increased risk of perioperative thrombosis. Blast transformation was observed in 16.3% of splenectomized patients, with no impact on postsplenectomy survival; blast transformation was more frequently related to a higher spleen volume and a lower platelet count.

Barosi et al[17] assessed 549 MF patients, 462 of whom had not undergone splenectomy and 87 of whom had. Splenectomy-related morbidity and mortality were 30% and 10%, respectively. In this study, leukemic transformation was 11.4% for nonsplenectomized patients and 26.4% for patients who had undergone splenectomy ($P < .001$). Before splenectomy, platelet count $< 100 \times 10^9$/L and the presence of blasts in peripheral blood at diagnosis were independent risk factors predictive of leukemic transformation. This study suggests that there is an increased risk of blast transformation in patients undergoing splenectomy, with this risk appearing to be independent of factors related to the indication to surgery.

Splenectomy was found to result in a rapid, albeit temporary, reduction in the number of circulating $CD34^+$ hematopoietic progenitor cells in 13 patients with primary MF included in a 1-year longitudinal study.[20] There also appeared to be an inverse correlation between the rate of clearance of $CD34^+$ cells and spleen volume. Furthermore, the percentage of $CD34^+$ $CXCR4^+$ splenic cells in peripheral blood was significantly lower before splenectomy but increased over the first month after splenectomy; a rapid decrease of these cells was observed within 6 months of splenectomy. The authors suggested that this temporary event may have been due to the (re)activation of new locations of hematopoiesis, occurring in either the bone marrow or other extramedullary sites (ie, liver or lungs).

The underlying disease and its natural progression appear to affect long-term complications of splenectomy, such as blast transformation. It is possible that the apparent association of splenectomy with leukemic transformation may be due to a postsplenectomy redistribution of circulating blasts, as opposed to true clonal evolution, with no impact on overall survival.[4,18]

Impact of Splenectomy in Patients With MF Before Allogeneic HSCT

Because the splenic burden of disease can affect the success of transplantation, a tumor debulking procedure, such as splenectomy,

before HSCT seems attractive. However, there is currently a lack of prospective randomized clinical trials assessing the role of splenectomy before HSCT in MF patients. Results obtained from retrospective studies are controversial, and there is a lack of consensus on the role of splenectomy in improving transplant engraftment (Table 2).

A predictive pretransplantation scoring system was proposed after a retrospective analysis of 46 patients with primary MF, in which spleen size > 22 cm, a transfusion history of > 20 red blood cell units before transplantation, and alternative donor type were found to have a negative impact on transplant outcome by multivariate analysis.[28] For example, a significantly higher percentage of transplant-related mortality was found in patients with spleen size > 22 cm (27% vs. 9%; $P = .02$), and 5-year survival was significantly lower (33.3% vs. 68.2%; $P = .01$). While the impact of splenomegaly seems clear, the role of splenectomy is not.

Table 2 Splenectomy in Myelofibrosis Patients Before Allogenic Hematopoietic Stem-Cell Transplantation

Outcome	No. of Splenectomized Patients	Comments
Faster hematopoietic recovery		
Akpek 2013[21]	472	
Li 2001[3]	11	
Guardiola 1999[22]	27	
Patriarca 2019[23]	12	
Robin 2011[24]	55	
Stewart 2010[25]	17	Only for patients receiving RIC
No impact on hemopoietic recovery		
Ballen 2010[26]	65	
Robin 2017[27]	39	
No improvement in survival outcome		
Bacigalupo 2010[28]	28	
Akpek 2013[21]	472	Not only myelofibrosis
Stewart 2010[25]	17	
Guardiola 1999[22]	27	
Ballen 2010[26]	65	
Li 2001[3]	11	
Improvement in survival outcome		
Robin 2017[27]	39	Greater than EFS
Bacigalupo 2010[28]	28	RRD reduced only for patients with spleen size > 22 cm
Increased GVHD risk		
Akpek 2013[21]	472	Only in HLA-sibling–matched transplants
No impact on GVHD risk		
Guardiola 1999[22]	27	
Robin 2017[27]	39	

Abbreviations: EFS = event-free survival; GVHD = graft-versus-host disease; HLA = human leukocyte antigen; RIC = reduced-intensity conditioning; RRD = relapse-related death.

Although splenectomy was not predictive of survival in this study (crude survival was 46% vs. 55% in splenectomized and nonsplenectomized patients, respectively; $P = .5$), the authors investigated its role in patients with a larger spleen size. Relapse-related death was significantly reduced in patients with a large spleen (> 22 cm) who had undergone splenectomy compared to nonsplenectomized patients (13% vs. 56%; $P = .02$). Hence, splenectomy performed in patients with a larger spleen size reduced relapse-related death without any advantage in terms of transplant-related mortality or survival, independent of spleen size. Considering that the spleen contains a significant tumor load in primary MF patients, when the spleen is very large, a positive role of splenectomy would be expected.

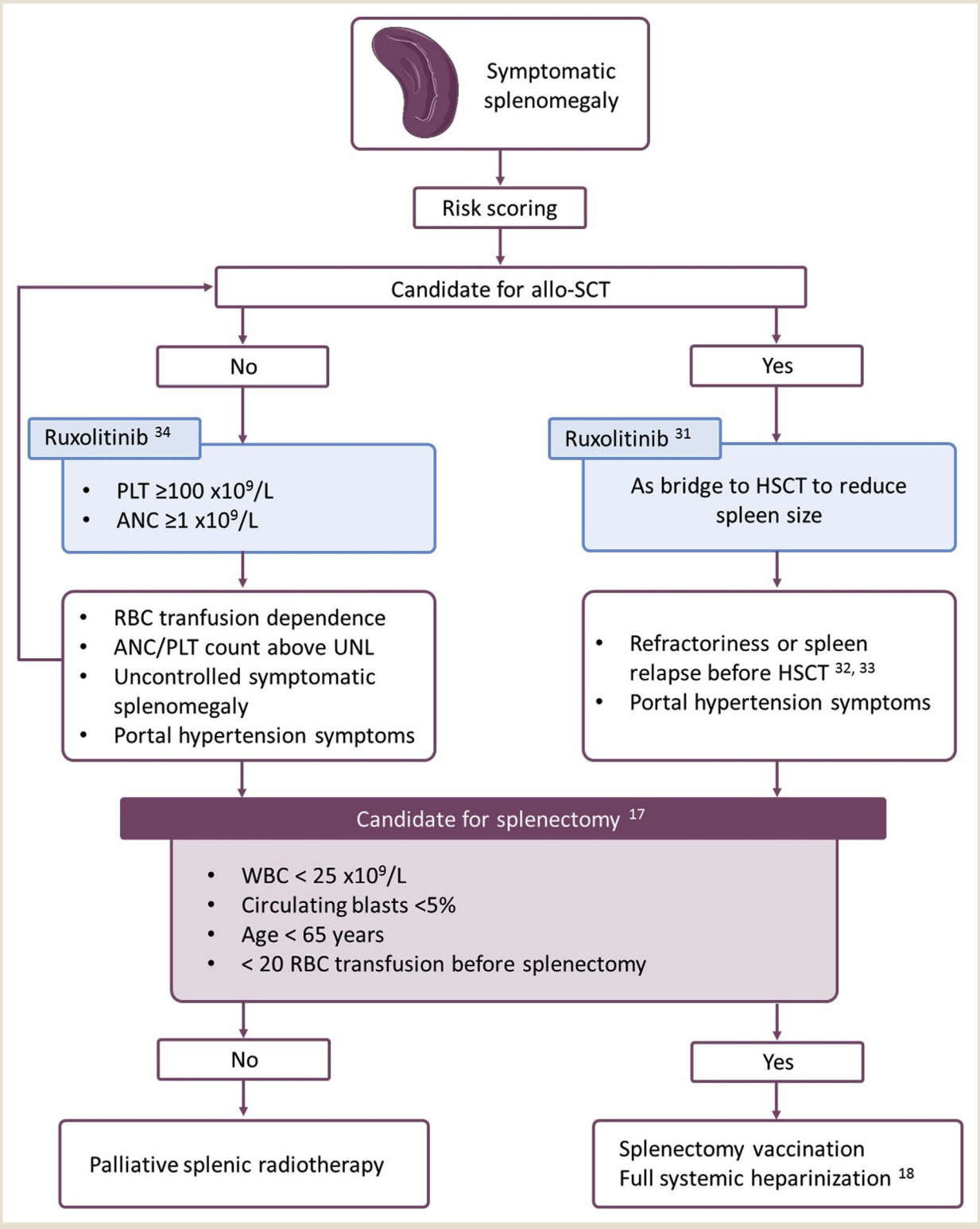
A large retrospective study analyzed 9683 patients who received HSCT for chronic myeloid leukemia, other myeloproliferative disorders including MF, and myelodysplastic syndrome, dividing the patients on the basis of spleen status before HSCT as follows: 472 had prior splenectomy, 300 received splenic irradiation, 1471 had splenomegaly, and 7440 had normal spleen size.[21] Among these groups, on the one hand, patients with splenomegaly had a decreased probability of neutrophil engraftment at day 28 and a longer time of neutrophil engraftment compared to patients with normal spleen. On the other hand, patients who had prior splenectomy had earlier neutrophil and platelet engraftment compared to patients with normal spleen, and had the highest probability of neutrophil engraftment at day 28. Across all groups, neutrophil engraftment at day 28 was experienced by only 77% of patients who had received splenic irradiation compared to 90% of patients with prior splenectomy. There were no differences identified across the groups in terms of the long-term outcome of engraftment at day 100. Multivariate analysis showed no statistically significant difference in acute graft-versus-host disease (GVHD) or overall mortality among the groups on the basis of spleen status. Prior splenectomy increased the risk of chronic GVHD only in human leukocyte antigen (HLA)-sibling–matched transplants, whereas splenomegaly was significantly associated with increased risk of chronic GVHD in HLA-mismatched transplant recipients.

Li et al[3] retrospectively evaluated 26 patients with MF, including 11 patients who had undergone splenectomy before HSCT and 15 nonsplenectomized patients. In this analysis, patients with splenectomy had faster neutrophil recovery after HSCT compared to nonsplenectomized patients, whereas splenectomy showed no significant advantage or disadvantage for other posttransplantation outcomes.

Pretransplantation splenectomy and the absence of osteomyelosclerosis were associated with a shorter time to neutrophil and platelet recovery in a retrospective multicenter study of 55 patients who underwent allogeneic HSCT for MF.[22] However, GVHD incidence and survival were not influenced by splenectomy.

The Gruppo Italiano Trapianti di Midollo Osseo (GITMO) presented data of a phase 2 randomized trial comparing two different conditioning regimens (busulfan or thiotepa associated with fludarabine) in high-risk MF patients.[23] Among the 57 allografted patients, spleen status at transplantation significantly influenced hematopoietic recovery. Significantly slower neutrophil and platelet engraftment were reported in patients with splenomegaly (19 and 20 days, respectively) compared to previously

Figure 1 Algorithm for Splenectomy and Radiotherapy Indications and Timing in Myelofibrosis



Abbreviations: ANC = absolute neutrophil count; HSCT = hematopoietic stem-cell transplantation; Plt = platelet; RBC = red blood cell count; WBC = white blood cell count.

splenectomized patients or those with a normal spleen size (16 and 14 days, respectively; $P < .0001$).

The British Society for Blood and Marrow Transplantation published retrospective data from 51 patients with MF who underwent HSCT.[25] In the reduced-intensity conditioning group, previous splenectomy reduced time to engraftment (13 vs. 20 days; $P = .008$) without affecting other transplant-related outcomes.

In a retrospective analysis of transplantation outcomes of 289 patients who received HSCT for primary MF between 1989 and 2002 from the Center for International Bone Marrow Transplant Research (CIBMTR) database, graft failure did not appear to be influenced by spleen status at the time of HSCT.[26] In patients with splenomegaly, graft failure was 13.3%, compared to 13.2% for patients without splenomegaly and 15.3% for patients who had undergone a prior splenectomy. However, the spleen size and method of determination of splenomegaly were not reported; transplant centers reported splenomegaly only as present or absent. In addition, the median time for engraftment was not significantly influenced by splenomegaly, and multivariate analysis showed that both splenomegaly and prior splenectomy were not predictive of disease-free survival.

Therefore, even if the majority of reported studies identify a role for splenectomy in reducing the time for neutrophil and platelet recovery, this effect does not appear to have an impact on transplant-related outcome. Furthermore, the specific role of splenectomy in improving transplant outcomes is even less clear.

An analysis of 85 patients with MF, 39 splenectomized before HSCT and 46 not splenectomized, showed no difference in the risk of relapse, nonrelapse mortality, or death between treatment groups.[27] Multivariate analysis showed pretransplantation splenectomy was associated with improved event-free survival and overall survival (hazard ratio, 0.52; 95% confidence interval, 0.29-0.95; $P = .034$), suggesting splenectomy might have a protective effect. Although the rate and time for neutrophil and platelet engraftment were similar in the two groups, 50% of splenectomized patients developed postsurgical complications, most frequently hemorrhage and thrombosis. The authors concluded that pretransplantation splenectomy did not have a deleterious impact on post-transplantation outcomes in some patients with huge splenomegaly.[27]

An analysis from the Société Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) on 147 patients with MF who had undergone HSCT between 1997 and 2008 showed that splenectomy before HSCT improved engraftment (92% vs. 87% for nonsplenectomized patients; $P = .008$) and had a favorable impact on overall survival in men.[24]

Without an evident survival benefit, the decision to undergo pretransplantation splenectomy should be assessed on an individual basis; it may be justified in symptomatic patients with massive splenomegaly.[29]

The ability of JAK inhibitors to induce spleen response, thereby potentially reducing engraftment time, makes these drugs appealing elements of the pre–allogenic HSCT management.[30,31] Safety and efficacy data in this setting are now available and are further increasing; the optimal timing of transplant for eligible patients should be at the time of best response to JAK inhibitors.[30] Therefore, the role of pretransplantation splenectomy will be further reduced to those patients with splenomegaly that cannot be controlled with medical therapy.[32,33]

Conclusion

Splenectomy may offer an effective therapeutic option for treating massive splenomegaly and/or cytopenias in patients with MPNs, especially in patients with a poor response after conventional medical treatment. Figure 1 provides an algorithm that summarizes and defines the possible indications and timing for splenectomy and splenic radiotherapy during the clinical course of MF.[18,19,31,33,34] The benefits of splenectomy, however, must be weighed against the substantial risk of short- and long-term complications and morbidity. Although splenectomy is not routinely performed before transplantation, it may be appropriate in patients with massive splenomegaly and related symptoms, so long as the higher risk of graft failure in such cases is taken into account.

The most common complications postsplenectomy are bleeding, thrombosis, and infections, and may occur in up to 30% of patients. The risk of thrombosis may be reduced by proactive prophylaxis with low-molecular-weight heparin after surgery; rate of bleeding does not differ significantly among patients receiving prophylaxis. However, fatal complications may occur in up to 8% of surgeries, mainly due to infections and bleeding (Table 1). Older age, thrombocytopenia (range, 50-100 $\times$ 10^9/L), circulating blasts, leukocytosis ($> 25 \times 10^9$/L), and hypocellular bone marrow have been identified as risk factors for an unfavorable outcome after splenectomy.

It is imperative that splenectomy is used cautiously and only in highly selected patients (ie, those with severe, refractory cytopenia and extremely large symptomatic splenomegaly whose disease has failed to respond to optimal therapeutic management). Moreover, the recent approval of JAK1/2 inhibitors for patients with MF has reduced the role of splenectomy. Splenic irradiation may also be considered to reduce spleen size, but its effect is generally short lasting, and the risk of severe and long-term cytopenias may be a deterrent.

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