

Hypertrophic and Dilated Cardiomyopathy

Long-Term Effects of Surgical Septal Myectomy on Survival in Patients With Obstructive Hypertrophic Cardiomyopathy

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OBJECTIVES	This study sought to determine the impact of surgical myectomy on long-term survival in hypertrophic cardiomyopathy (HCM).
BACKGROUND	Left ventricular (LV) outflow tract obstruction in HCM increases the likelihood of heart failure and cardiovascular death. Although surgical myectomy is the primary treatment for amelioration of outflow obstruction and advanced drug-refractory heart failure symptoms, its impact on long-term survival remains unresolved.
METHODS	Total and HCM-related mortality were compared in three subgroups comprised of 1,337 consecutive HCM patients evaluated from 1983 to 2001: 1) surgical myectomy (n = 289); 2) LV outflow obstruction without operation (n = 228); and 3) nonobstructive (n = 820). Mean follow-up duration was 6 ± 6 years.
RESULTS	Including two operative deaths (procedural mortality, 0.8%), 1-, 5-, and 10-year overall survival after myectomy was 98%, 96%, and 83%, respectively, and did not differ from that of the general U.S. population matched for age and gender (p = 0.2) nor from patients with nonobstructive HCM (p = 0.8). Compared to nonoperated obstructive HCM patients, myectomy patients experienced superior survival free from all-cause mortality (98%, 96%, and 83% vs. 90%, 79%, and 61%, respectively; p < 0.001), HCM-related mortality (99%, 98%, and 95% vs. 94%, 89%, and 73%, respectively; p < 0.001), and sudden cardiac death (100%, 99%, and 99% vs. 97%, 93%, and 89%, respectively; p = 0.003). Multivariate analysis showed myectomy to have a strong, independent association with survival (hazard ratio 0.43; p < 0.001).
CONCLUSIONS	Surgical myectomy performed to relieve outflow obstruction and severe symptoms in HCM was associated with long-term survival equivalent to that of the general population, and superior to obstructive HCM without operation. In this retrospective study, septal myectomy seems to reduce mortality risk in severely symptomatic patients with obstructive HCM. (J Am Coll Cardiol 2005;46:470-6) © 2005 by the American College of Cardiology Foundation

Left ventricular (LV) outflow tract obstruction is an important pathophysiologic component of hypertrophic cardiomyopathy (HCM) and an independent determinant of

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progressive heart failure disability and cardiovascular death (1-7). Indeed, the presence of outflow obstruction has been a prerequisite for major therapeutic interventions to relieve severe drug-refractory heart failure symptoms (1-3,6).

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Surgical septal myectomy has been performed effectively for over 40 years as the primary treatment strategy for such HCM patients of all ages, with substantial long-term hemodynamic and symptomatic benefits attributable to the operation (8-28). However, a major unresolved issue concerns whether surgical myectomy, often performed in relatively young patients, has a beneficial impact on long-term survival. A unique aspect of this study is the opportunity to compare long-term outcome in a large surgical series with that in a cohort of medically managed HCM patients, as well as the expected survival in the general population, to determine whether surgical relief of LV outflow obstruction by myectomy has clinical benefit beyond improvement in the quality of life.

METHODS

Selection of patients. The study population of 1,337 consecutive HCM patients is composed of three retrospec-

Abbreviations and Acronyms

HCM = hypertrophic cardiomyopathy
LV = left ventricle/ventricular
NYHA = New York Heart Association

tively identified subgroups evaluated from 1983 to 2001: 289 patients with isolated surgical ventricular septal myectomy at Mayo Clinic; 64 other patients with myectomy during this period who had additional operative procedures performed concomitantly (e.g., valve replacement, coronary artery bypass grafting) were excluded. The Mayo Clinic is a long-standing tertiary HCM center with patients referred on a national basis, and has maintained a special expertise in performing the septal myectomy operation for over 40 years. Comparison subgroups totaling 1,048 nonoperated HCM patients were included in this study: 1) 228 patients with left ventricular outflow obstruction ≥ 30 mm Hg at rest; these patients had not been recommended for myectomy largely because of insufficiently advanced symptoms or because of ongoing medical treatment for severe functional limitation; and 2) 820 patients without outflow obstruction who, by convention, were not considered candidates for surgery. These two comparison groups were assembled from three other HCM centers with large cohorts but not with specialized surgical experience in this disease (Minneapolis Heart Institute Foundation; Azienda Ospedaliera Careggi, Florence, Italy; and Federico II University of Naples, Italy). Selected clinical data from these 1,048 patients have been included in a prior report (4).

The most recent vital status was obtained for each of the 1,337 study patients by clinic visit or mailed questionnaire. This study received approval by institutional review board (or its equivalent) at each participating center.

Echocardiography. The diagnosis of HCM was based on the presence of a hypertrophied nondilated LV in the absence of other diseases capable of producing the magnitude of the hypertrophy evident (29). Echocardiographic parameters were measured as previously described (4,29). The LV outflow tract gradient was assessed under resting (basal) conditions, using continuous wave Doppler echocardiography (4,29), at the initial evaluation in the participating institution (or just before myectomy), and also 3.2 ± 3 years after myectomy.

Surgery. Criteria for surgical intervention at the Mayo Clinic were LV outflow obstruction ≥ 50 mm Hg at rest or with provocative maneuvers attributable to systolic anterior motion of the mitral valve, associated with New York Heart Association (NYHA) functional classes III to IV limitation (or repetitive and disabling effort-related syncope) despite maximum medical management (6,7,24). The septal myectomy operation in the present cohort was predominantly that described by Morrow *et al.* (8,10,11). This procedure, performed through an aortotomy, creates a rectangular trough via two parallel longitudinal incisions in the basal

septum. Incisions are connected proximally below the aortic valve and extended distally just beyond the level of mitral-septal contact and subaortic obstruction, or in some patients to the base of the papillary muscles (i.e., extended myectomy).

Statistical analysis. Data are expressed as mean \pm SD. One-way analysis of variance was used to compare normally distributed data. Noncontinuous data were analyzed using chi-square tests. The *p* values are two-sided; *p* < 0.05 was considered statistically significant.

The survival analysis model used proportional hazards regression methodology; Kaplan-Meier survival curves were compared using log-rank statistics. End points were all-cause mortality and HCM-related mortality. Deaths within 30 days after myectomy were considered operative deaths and are included in both end points. The HCM mortality included sudden cardiac death (unexpected within 1 h of witnessed collapse or nocturnal), heart failure death (in context of progressive cardiac decompensation), and stroke-related death (30). Appropriate discharges from implantable defibrillators for ventricular fibrillation or sustained ventricular tachycardia (*n* = 8) were regarded as sudden deaths (30). Survival was censored at cardiac transplantation in 9 patients with end-stage heart failure and at the time of percutaneous septal ablation in 20 nonoperated patients with LV outflow obstruction.

Follow-up for nonoperated HCM patients began at the initial clinical evaluation at the participating institution. For myectomy patients, follow-up began on the day of operation (4.8 ± 12 months after initial evaluation). Mean follow-up duration was 6.2 ± 6 years.

To determine whether differences in survival between the myectomy and the other nonoperated HCM groups could be explained by disease-related variables other than the operation, univariate and multivariate Cox proportional hazard regression analyses were performed (Table 1). Statistically significant variables from the univariate analysis were entered stepwise into the multivariate regression model.

For comparison with myectomy patients, an expected survival curve for the general population was generated from U.S. Health Statistics, which incorporate all-cause mortality (31). Each myectomy patient was matched to the U.S. white population by age, gender, and year of study entry.

RESULTS

Baseline characteristics. Myectomy and nonoperated obstructive HCM patients were similar with respect to the initial LV outflow gradient at rest (67 vs. 68 mm Hg, respectively; *p* = 0.9) (Table 1). Myectomy patients were younger (45 vs. 50 years; *p* = 0.01) and had larger left atrial (47 vs. 45 mm; *p* = 0.001) and LV end-diastolic cavity dimensions (44 vs. 42 mm; *p* = 0.001). Because advanced symptoms refractory to pharmacologic therapy represent the standard indication for operation, myectomy patients ex-

Table 1. Baseline Clinical and Demographic Data in Three Hypertrophic Cardiomyopathy Patient Subgroups

Parameter	All Patients (n = 1,337)	Myectomy (n = 289)	Nonoperated Obstructive* (n = 228)	Nonobstructive (n = 820)	ANOVA p Value
Age (yrs)	45.3 ± 20	45.3 ± 19†	50.0 ± 22	44.0 ± 19	<0.001
Male gender	779 (58)	148 (51)	106 (46)	525 (64)	<0.001
NYHA functional class (at entry)					
Mean	1.83 ± 0.9	2.89 ± 0.7†	1.74 ± 0.8	1.49 ± 0.6	<0.001
I	608 (45)	22 (7)†	98 (43)	488 (60)	—
II	380 (28)	11 (4)†	95 (42)	274 (33)	—
III to IV	348 (26)	256 (89)†	34 (15)	58 (7)	—
Atrial fibrillation	259 (19)	59 (20)	56 (25)	144 (18)	0.05
CAD-documented medications	41 (3)	10 (3)	10 (4)	21 (3)	0.33
Beta-blocker	570 (43)	173 (60)	125 (55)	272 (33)	<0.001
Calcium-blocker	466 (35)	116 (40)	92 (40)	258 (31)	0.005
Disopyramide	56 (4)	31 (11)	14 (6)	11 (1)	<0.001
Amiodarone	154 (12)	12 (4)†	30 (13)	112 (14)	<0.001
Echocardiography					
Max LV thickness (mm)	22.5 ± 6	23.5 ± 7	23.7 ± 7	21.8 ± 6	<0.001
LA diameter (mm)	42.9 ± 9	47.4 ± 8†	44.6 ± 8	41.4 ± 8	<0.001
LVEDD (mm)	43.5 ± 7	43.9 ± 7†	41.5 ± 6	43.9 ± 7	<0.001
LV outflow gradient (at rest) (mm Hg)	29.2 ± 39	67.3 ± 41	68.0 ± 31	5.1 ± 7	—
Severe MR	71 (5)	21 (7)	24 (8)	26 (3)	<0.001
Follow-up					
Duration	6.2 ± 6	5.8 ± 4‡	4.9 ± 5	6.6 ± 6	0.001
Mode of death					
Sudden	47 (4)	5 (2)	16 (7)	26 (3)	—
Heart failure	33 (2)	2 (<1)	10 (4)	21 (3)	—
Stroke	14 (1)	0	6 (3)	8 (1)	—
Non-cardiac	71 (5)	16 (5)	22 (10)	37 (5)	—
Operative	2 (<1)	2 (<1)	0	0	—

*Obstruction defined as peak instantaneous left ventricular (LV) outflow gradient ≥30 mm Hg under resting conditions. Data are expressed as mean ± standard deviation or as number of patients with percentage in parentheses. †p < 0.01 and ‡p < 0.05 for comparison of myectomy versus nonoperated obstructive groups.

ANOVA = analysis of variance; CAD = coronary artery disease; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; Max = maximal; MR = mitral regurgitation; NYHA = New York Heart Association.

pectedly showed more severe functional disability at study entry: 89% in NYHA functional classes III to IV compared with 15% in the nonoperated obstructive HCM group (p < 0.001).

Clinical benefits of myectomy. The surgical myectomy group experienced substantial symptomatic and hemodynamic improvement after myectomy; 255 (89%) patients were in NYHA functional classes III to IV before operation, whereas only 12 (6%) were in classes III to IV at the most recent follow-up. The mean functional class was 2.9 ± 0.7 before myectomy and 1.5 ± 0.7 at last postmyectomy follow-up (p < 0.001). The average preoperative outflow gradient at rest was 67 ± 41 mm Hg, and decreased to 3 ± 8 mm Hg postoperatively (p < 0.001). Nonfatal complications included ventricular septal defect in two patients (0.8%) and complete heart block requiring permanent pacemaker in three (1%).

Survival after myectomy. There were 25 deaths after myectomy, including 2 related to operation (operative mortality, 0.8%); both operative deaths involved patients with NYHA functional class IV heart failure who underwent emergency myectomy at 64 and 71 years of age. Seven other deaths were probably or definitely caused by HCM (5 sudden deaths and 2 due to heart failure), and 16 were noncardiac deaths. Mean age at death was 64 ± 12 years

(range, 22 to 82 years), occurring 6.8 ± 5 years (range, 0.2 to 17 years) after myectomy.

The 1-, 5-, and 10-year overall survival after myectomy was 98%, 96%, and 83%, respectively, and did not differ from the age- and gender-matched general population (98%, 95%, and 88%, respectively; log-rank p = 0.2) (Fig. 1).

Survival comparisons in patients with obstructive HCM. Among patients with LV outflow tract obstruction (n = 517), overall survival of myectomy patients was significantly better than that of nonoperated obstructive HCM patients (98%, 96%, and 83% vs. 90%, 79%, and 61% at 1, 5, and 10 years, respectively; log-rank p < 0.001) (Fig. 2). Baseline parameters with significant univariate association to improved survival included myectomy (p < 0.001), male gender (p = 0.01), younger age (p < 0.001), lower NYHA functional class (p = 0.001), absence of atrial fibrillation (p = 0.02), and absence of documented coronary artery disease (p = 0.03). With these variables entered into the multivariate model, the only independent predictors of improved survival were myectomy (hazard ratio [HR] 0.43, p < 0.001) and younger age at study entry (HR 0.97 per year decrement of age; p < 0.001).

Similarly, survival free from HCM-related death was also superior in myectomy patients compared with nonoperated

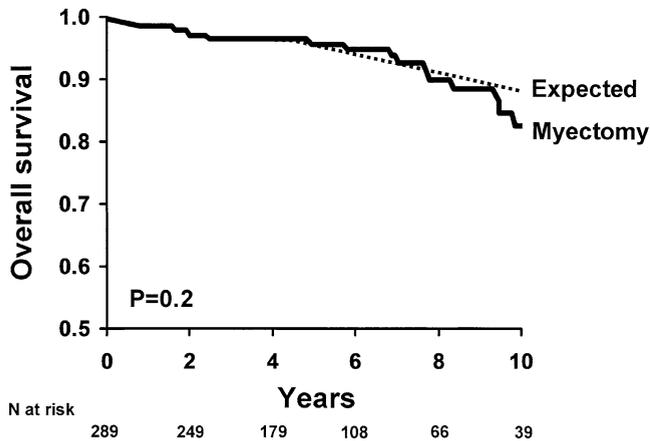


Figure 1. Survival free from all-cause mortality after surgical myectomy for obstructive hypertrophic cardiomyopathy (n = 289) compared with the age- and gender-matched general U.S. white population. Log-rank, p = 0.2.

obstructive HCM patients (99%, 98%, and 95% vs. 94%, 89%, and 73%, respectively; log-rank p < 0.001) (Fig. 3). Multivariate analysis showed that only myectomy (HR, 0.09; p = 0.001) and smaller left atrial dimension (HR 0.94 per ml decrement; p = 0.003) were independently associated with HCM-related survival.

Myectomy patients also showed a significantly lower risk specifically for sudden cardiac death compared with nonoperated obstructive HCM patients (100%, 99%, and 99% vs. 97%, 93%, and 89%, respectively; HR = 0.27; log-rank p = 0.003) (Fig. 4).

Survival comparisons including obstructive and nonobstructive HCM patients. Compared with nonobstructive patients (overall survival 98%, 95%, and 87%, respectively; HCM-related survival 98%, 96%, and 91%, respectively), the myectomy patients showed statistically indistinguishable overall survival (p = 0.8) (Fig. 2), but superior HCM-related survival (p = 0.01) (Fig. 3). Multi-

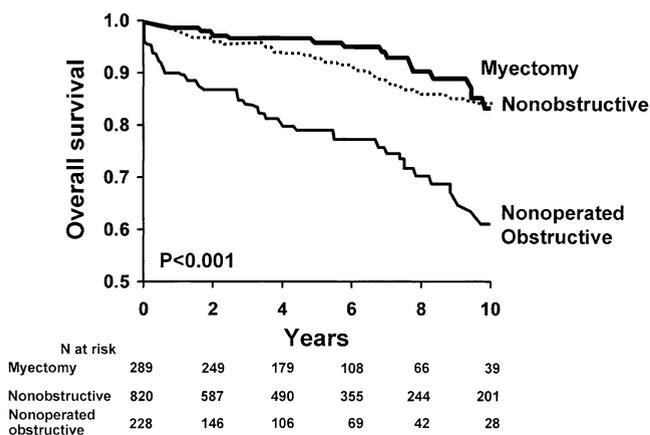


Figure 2. Survival free from all-cause mortality in three hypertrophic cardiomyopathy patient subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p < 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.8.

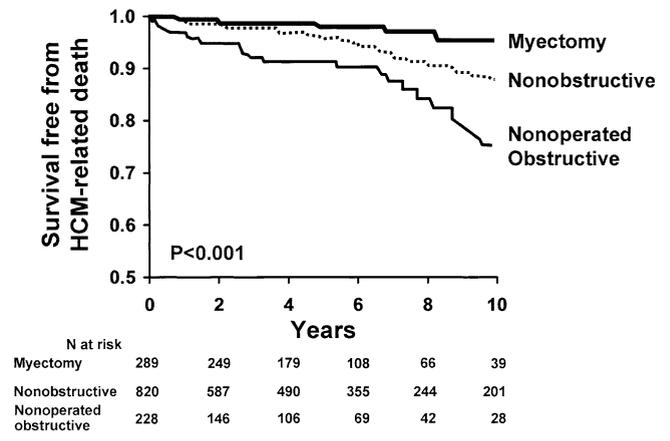


Figure 3. Survival free from hypertrophic cardiomyopathy-related death among patients in three hypertrophic cardiomyopathy (HCM) subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p < 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.01.

variate analysis including all three study groups (n = 1,337) confirmed that myectomy had a strong, independent association with both overall (p < 0.001) and HCM-related survival (p = 0.01).

When confining the analysis to those patients ≤45 years old at study entry, thereby reducing the potentially confounding age-related co-morbidities such as coronary artery disease, patients treated with surgical myectomy continued to show significantly better survival than nonoperated obstructive HCM patients (overall survival HR 0.28; p < 0.001; HCM-related survival HR 0.25; p = 0.004). The 1-, 5-, and 10-year survival after myectomy was 99%, 98%, and 92%, respectively, as compared with 92%, 88%, and 75%, respectively (log-rank p = 0.006) for the nonoperated obstructive HCM patients.

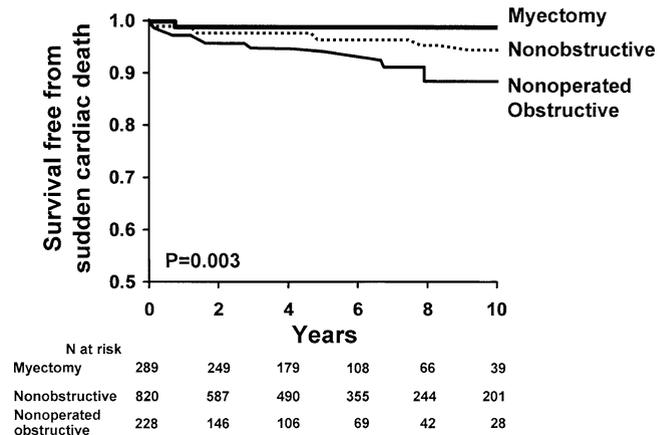


Figure 4. Survival free from sudden cardiac death among patients in three hypertrophic cardiomyopathy subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p = 0.003; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p = 0.003; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.3.

DISCUSSION

Based on over four decades of worldwide experience, and the recent American College of Cardiology-European Society of Cardiology Expert Consensus Guidelines, septal myectomy is considered the gold-standard strategy for the relief of drug-refractory symptoms in HCM patients with LV outflow obstruction (1-3,5-7). Septal myectomy, by virtue of abolishing LV outflow obstruction and mitral regurgitation and normalizing intracardiac pressures, wall stress, myocardial oxygen demand, metabolism, and coronary flow, has been shown consistently to improve both exercise capacity and quality of life (12,15,24). Because of the cumulative experience and improved myocardial protection techniques, operative mortality associated with myectomy has diminished dramatically from the initial surgical reports. At present, procedural risk is <1% to 2% at experienced centers, and, in fact, has approached zero in the most recent patients (6,17,20,22,23,27,32-36).

Whether the salutary hemodynamic and clinical effects of myectomy translate into enhanced long-term postoperative survival remains unresolved. Clarification of this pivotal issue has been impeded by certain insurmountable practical and ethical obstacles implicit in performing prospective, randomized trials comparing myectomy with other treatment strategies in severely symptomatic patients. These include the well-documented efficacy of myectomy for relieving symptoms, the relative infrequency with which this operation is performed (i.e., $\leq 5\%$ of all HCM patients) (2,5,6), and the particularly long-term follow-up that would be required. It is unlikely that such trials will ever take place.

The present study provides the strongest evidence to date showing that surgical relief of obstruction may improve long-term survival. Although this study is necessarily retrospective, we have taken the unique opportunity to assess long-term outcome after septal myectomy in one of the longest-standing and continuous surgical referral programs (7,14,24). Outcomes were compared with an age- and gender-matched general U.S. population, and to recently available cohorts of nonoperated HCM patients (4). Taken together, these data afford substantial evidence of favorable (possibly enhanced) long-term survival after surgical myectomy.

Long-term survival free from HCM-related mortality after myectomy was excellent (95% at 10 years). Furthermore, the 10-year overall postoperative survival free from all-cause mortality did not differ from that of the general population, suggesting that myectomy may afford patients the opportunity to achieve normal or near-normal longevity. This observation is of particular relevance given the youthful age (mean, 45 years) of the operated patients. Notably, the comparison group of patients with LV outflow obstruction who did not undergo myectomy experienced a much less favorable outcome with greater

than twice the overall mortality risk observed in myectomy patients. These data also suggest that the likelihood of sudden death was reduced after myectomy (compared with nonoperated patients); however, the events were not abolished after operation, indicating that independent risk stratification is still required for patients undergoing this procedure (2,4,6,7).

Unavoidably, rigorous matching of myectomy and nonoperated patients was not possible. Nevertheless, we regard the statistical comparisons and derived conclusions valid and clinically relevant. First, the postoperative survival of myectomy patients was indistinguishable from that of the general population. Second, the multivariate analyses clearly identified myectomy as a strong, independent determinant of survival, substantiating that the differences in long-term survival documented here are likely attributable to surgical relief of the subaortic gradient. Third, despite significantly more advanced preoperative symptoms, myectomy patients nevertheless showed long-term survival that greatly exceeded that of the less symptomatic nonoperated obstructive HCM patients. Fourth, analysis of patients ≤ 45 years old, reducing the potential for confounding age-related variables, showed nearly identical results to the primary analysis with a greater than three-fold increase in risk of mortality among obstructive HCM patients managed without surgery.

The operative results reported here represent those achieved by an experienced surgical referral center and therefore constitute a measure of the most favorable outcome that can be expected from septal myectomy (6,7,16,24). Indeed, we believe that this surgical series was most relevant to understanding the optimal benefits that can be achieved with surgical intervention in drug-refractory, severely symptomatic patients with obstructive HCM. However, it is inappropriate to extrapolate these findings to low-volume surgical centers or alternative treatment modalities such as catheter-based alcohol septal ablation, for which follow-up is comparatively brief and post-procedural outcome is incompletely defined (6,35-37). In addition to showing an impressive survival advantage for myectomy, our data also support the standard recommendation to intervene in obstructive HCM patients (with myectomy, or selectively with alternatives such as alcohol septal ablation) when refractory heart failure symptoms have progressed to NYHA functional classes III to IV (6,7,24). However, we do not regard as prudent using these data to justify or promote earlier major interventions with more lenient eligibility criteria in mildly symptomatic patients.

Survival analysis designs that include surgical patients can be problematic in part because by definition surgical patients have 100% survival up to the date of operation, and operative candidates who die while awaiting operation are not included in the analysis. The survival analysis presented in this study was judged to be the most

appropriate and reliable model for these purposes. However, we had prospectively identified two additional survival analysis models. The first alternative model excluded all deaths in the nonoperated comparison HCM groups that occurred within six months of study entry. The second alternative strategy treated myectomy as a time-dependent variable with all operated and nonoperated patients having the same study entry point, i.e., the date of first evaluation at each participating center. Most importantly, both of these alternative analyses yielded substantially the same outcome results as the survival model used in the present study.

We prospectively defined cardiac events and the statistical methodology based on precedent, and our judgment that this strategy appropriately reflected the clinical scenario studied here. Nonetheless, to examine whether our event definitions unduly influenced the results, we retrospectively reanalyzed the data with implantable cardioverter-defibrillator discharge and alcohol septal ablation considered as inconsequential (non-events) and cardiac transplantation considered as a surrogate for cardiac death. With these alternative definitions, the survival results were unchanged from the principal analysis presented in the report.

In conclusion, the data presented here offer considerable evidence showing that surgical myectomy in patients with obstructive HCM not only vastly improves quality of life, but also enhances survival over that that would otherwise be expected as a consequence of longstanding LV outflow tract obstruction. In accord with contemporary consensus panel recommendations (6), the present findings support septal myectomy as the primary treatment for HCM patients with severe drug-refractory symptoms caused by LV outflow obstruction.

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