

Cardiac Surgery With Extracorporeal Circulation in Cancer Patients: Influence on Surgical Morbidity and Mortality, and on Survival

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Introduction and objectives. Morbimortality related to cardiac surgery may be superior in patients with malignancy neoplastic disease. Inflammatory phenomena and immunologic changes secondary to extracorporeal circulation use can also increase tumor recurrence. We evaluate characteristics and results of cardiac surgery in our neoplastic patients.

Methods. Out of 2146 consecutive patients who underwent cardiac surgery with extracorporeal circulation, 89 (4.2%) had been previously affected by cancer. Cancer was active (recent diagnosis or under treatment) in 33 patients (group A) and in 56 (group B) were in remission. Both groups were matched with 165 patients with no tumor, according to age, gender, type of surgery, and comorbidity (group C). We retrospectively evaluated incremental risk factors for surgical morbimortality, survival, and tumor recurrence.

Results. Median interval between cancer diagnosis and surgery was 60 months and mortality and morbidity were 4.5% and 36%, respectively, versus 5.4% and 32.7% in group C. During follow-up, 12 patients died (8 due to cancer), 16 suffered cancer recurrence, and 2 new tumors were diagnosed. Statistical analysis did not permit us to identify any incremental risk factor for mortality. Postoperative morbidity was increased in case of preoperative renal failure. During follow-up, survival was significantly decreased in group A, in case of preoperative left ventricular dysfunction or obstructive pulmonary disease, and when interval between cancer diagnosis and cardiac surgery was under 2 years.

Conclusions. We have not observed an increase in cardiac surgery morbimortality in cancer patients. Anyway, survival is decreased in case of active or recently diagnosed cancer.

Key words: Cancer. Extracorporeal circulation. Cardiac surgery.

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Cirugía cardíaca con circulación extracorpórea en pacientes oncológicos: influencia en la morbimortalidad quirúrgica y la supervivencia

Introducción y objetivos. La morbimortalidad de la cirugía cardíaca parece ser mayor en los pacientes neoplásicos. Los fenómenos inflamatorios y las reacciones inmunitarias secundarias a la circulación extracorpórea pueden favorecer la recidiva tumoral. Evaluamos las características y los resultados de la cirugía cardíaca en nuestros pacientes oncológicos.

Métodos. De 2.146 pacientes consecutivos sometidos a circulación extracorpórea, 89 (4,2%) presentaban una neoplasia. El cáncer estaba activo (recientemente diagnosticado o en tratamiento) en 33 pacientes (grupo A) y en remisión completa en 56 (grupo B). Se pareó ambos grupos con 165 pacientes sin tumor similares en edad, sexo, tipo de cirugía y comorbilidad (grupo C). Evaluamos retrospectivamente los factores de riesgo de morbimortalidad quirúrgica, supervivencia y recidiva tumoral.

Resultados. La mediana del intervalo entre diagnóstico del cáncer y cirugía fue de 60 meses, con mortalidad y morbilidad hospitalarias del 4,5 y el 36%, respectivamente, frente al 5,4 y el 32,7% en el grupo C. Durante el seguimiento, fallecieron 12 pacientes (8 por causa tumoral), 16 sufrieron recidiva y 2, tumores nuevos. El análisis estadístico no permitió identificar ningún factor de riesgo de mortalidad. La morbilidad postoperatoria aumentó en pacientes con insuficiencia renal. Durante el seguimiento, la supervivencia disminuyó significativamente en el grupo A en caso de disfunción ventricular izquierda preoperatoria y enfermedad pulmonar obstructiva crónica y cuando el intervalo entre diagnóstico de cáncer y cirugía fue < 2 años.

Conclusiones. No hemos observado un incremento en la morbimortalidad de la cirugía cardíaca en pacientes oncológicos. No obstante, la supervivencia disminuye en neoplasias activas o de diagnóstico reciente.

Palabras clave: Cáncer. Circulación extracorpórea. Cirugía cardíaca.

ABBREVIATIONS

CI: confidence interval
 COPD: chronic obstructive pulmonary disease
 ECC: extracorporeal circulation
 HR: hazard ratio
 LVEF: left ventricular ejection fraction
 OR: odds ratio

INTRODUCTION

Increasingly aged population, early cancer diagnosis and new therapies that increased survival of patients with malignancies, favour the appearance of cancer patients who simultaneously have a cardiomyopathy requiring surgery. The benefits, principally in terms of long-term survival, and risks, have not yet been clearly established.¹⁻⁵

In our population, we evaluate the following characteristics of patients with cancer undergoing cardiac surgery with extracorporeal circulation (ECC) indicated for a cause other than the tumor: type of procedure required, morbidity and mortality, long-term survival, and incidence of tumor recurrence.

METHODS

From January 2003 to May 2007, 89 (4.2%) of 2146 consecutive patients operated with ECC in our center had a cancer diagnosis. After full preoperative oncologic evaluation (with tumor staging and survival prognosis), the decision on cardiac surgery was taken only if estimated short- or medium-term survival with respect to the cardiomyopathy that established the indication was less than that associated with the neoplasia. Depending on the tumor stage, we classified patients in 2 groups:

- Group A: patients with active cancer at the time of the intervention (33 patients). In 13 patients cancer diagnosis was recent and no anti-tumor treatment had yet been initiated. The remaining 20 patients were undergoing radiotherapy, chemotherapy, or hormone therapy, with or without previous resection surgery
- Group B: patients in complete remission (56 patients)

We matched both groups with a third (group C) consisting on 165 patients with no tumor undergoing cardiac surgery with ECC, with similar characteristics in terms of age, gender, surgery type, and comorbidity.

We retrospectively gathered data on patient demography, preoperative risk factors, characteristics of

the neoplasias, cardiac surgery type and in-hospital morbidity, and mortality. During follow-up, we evaluated mortality, readmission (caused by tumor, heart, or other etiology), incidence of tumor recurrence or appearance of new neoplasia during follow-up. In this period, data were obtained through out-patient clinical review and telephone interviews with survivors or their families and/or their oncologists.

Statistical analysis was conducted with SPSS 13.0S. Preoperative variables were compared using χ^2 and the Mann-Whitney *U* test. We analyzed risk factors and actuarial survival using Cox logistic regression proportional risk model and Kaplan-Meier test. A *P* value less than .05 was considered significant. To adjust the Cox model, we considered all preoperative variables found significant in the univariate analysis (chronic obstructive pulmonary disease [COPD], left ventricular dysfunction, interval between cancer diagnosis and surgery <2 years, and group according to tumor stage), and those with *P*<.15 (peripheral vascular disease), as well as age and gender.

RESULTS

Clinical characteristics, preoperative risk factors, and surgical procedure type in groups A, B, and C appear in Table 1 and the distribution of neoplasias, in Table 2.

Surgical Mortality, Postoperative Complications, and Hospital Stay

With a median interval between cancer diagnosis and surgery of 60 (1-480) months, in-hospital mortality of patients affected by some type of tumor was 4 (4.5%) patients (2 in group A and 2 in group B), all due to cardiac causes. In group C, in-hospital mortality was 5.4% (9 patients: 6 due to cardiac causes, 1 neurologic, 1 septic, and 1 respiratory). In the postoperative period, some type of complication appeared in 36% of patients with malignancy neoplastic disease (39.9% in group A and 33.9% in group B) and in 32.1% of patients in group C. Frequency and distribution are detailed in Table 3.

The statistical study has not enabled us to identify risk factors of surgical mortality in patients affected by cancer (groups A and B) and only preoperative kidney failure is identified as a risk factor for complications in the postoperative period (*P*=.004; odds ratio [OR] = 9.1; 95% confidence interval [CI], 1.8-46.4).

Mean hospital stay of patients with malignancy neoplastic disease was 12.2 (9.2) days, with intensive stay care of 3.6 (6.9) days. We did not find significant differences in length of hospitalization and stay in intensive care of this group of patients by comparison with group C (12.1 [11.3] and 4.2 [9] days, respectively) nor when comparing groups A and B (mean length of hospitalization, 13 [11.8] and 11.7 [7.2] days; stay in intensive care, 4.4 [10.2] and 3.1 [3.8] days, respectively).

TABLE 1. Preoperative Characteristics of Patients in Groups A, B, and C

Variable	Group A (n=33)	Group B (n=56)	Group C (n=165)	P
Age, median (interval), y	71 (50-84)	72 (50-81)	71 (50-85)	.32
Men, %	69.6	58.9	69	.35
High blood pressure, %	51.5	57.1	83.7	.09
Peripheral artery disease, %	9	17.8	16.9	.49
Diabetes, %	18.1	26.7	30.3	.35
Dyslipidemia, %	30.3	32.1	40.6	.35
Kidney failure, %	18.1	7.1	9	.20
Chronic obstructive pulmonary disease, %	15.1	8.9	18.7	.22
Stroke, %	9	5.3	6	.76
Unstable angina, %	18.1	8.9	20	.45
Preoperative NYHA functional class III-IV, %	57.5	55.3	61.8	.16
Sinus rhythm, %	57.5	64.5	76.3	.42
Moderate-severe left ventricular dysfunction, %	36.3	33.9	26	.60
Surgery, %				.96
Coronary	21.2	17.8	23	
Valvular	57.5	58.9	52.7	
Mixed (coronary+valvular)	21.2	23.2	24.2	
Mitral valve replacement	18.1	12.5	24.2	.12
Aortic valve replacement	45.4	53.7	44.8	
Mitral-aortic replacement	15.1	16	7.2	
Coronary grafts, mean (SD), n	2.2 (1.1)	2 (1.3)	2.5 (1.1)	.11
Urgent surgery,* %	15.1	7.1	17.5	.24
Postoperative complications, %	39.3	33.9	32.7	.76
Risk, mean (SD), Euroscore	7.3 (3.4)	6.6 (2.2)	7.2 (3.6)	.56
Adjusted risk, mean (SD), %	12.1 (18.7)	7.8 (6.7)	12.3 (14.4)	.09
LVEF, mean (SD)	53.1 (16.3)	54.8 (16.2)	54.5 (14.5)	.9

LVEF, left ventricular ejection fraction; SD indicates standard deviation.

*In the 24 h following the onset of acute symptoms.

Postoperative Mortality, Tumor Recurrence, and Readmission

We conducted a follow-up of 100% of the patients, with medians of 22 months for group A patients, 29.5 months for group B, and 36 months for group C (interval, 1-52 months). Actuarial survival of patients with malignancy neoplastic disease is shown in Figure 1; 12 died: 8 due to a progression of the cancer (with a mean interval from the intervention of 25.2 [15.9] months), 3 due to cardiac causes, and 1 of stroke. Deaths due to cancer were secondary to recurrence of a uterine tumor in complete remission 5 years earlier (1 patient) or progression of active neoplasias (7 patients) located in bladder (2), stomach (2), lung (1), breast (1), and colon (1); 16 (18.8%) patients had a recurrent tumor, with a mean time of reactivation of 9.3 (9.1) months after surgery: 9 belonged to group A and 7 to group B. In the first group, the mean time of reactivation was 6.7 (6.9) months and in the second, 12.1 (10.3) months. Of 9 patients belonging to group A with a recurrent tumor, in 4 patients the cancer was diagnosed in the 3 months prior to surgery. In 2 patients new tumors were diagnosed during follow-up.

In group C, 14 patients died (10 of cardiac causes, 3 of neumopathies, and 1 of neoplasia). We found a significant difference ($P=.002$) in cause of mortality in

this period between groups A (active tumor) and C (control) in favor of the tumor etiology in the former (77.7% and 8.3%) by comparison with cardiac causes

TABLE 2. Location of Cancer

Location	No.	%
Breast	16	17.9
Prostate	15	16.8
Colon	13	14.6
Bladder	11	12.3
Uterus	6	6.7
Chronic lymphoid leukemia	5	5.6
Non-Hodgkin's lymphoma	4	4.5
Larynx	4	4.5
Rectum	4	4.5
Stomach	2	2.2
Lung	1	1.1
Thyroid	1	1.1
Acute myeloid leukemia	1	1.1
Myelodysplastic syndrome	1	1.1
Pharynx	1	1.1
More than 1 cancer		5.5
Lung+colon	1	
Bladder+prostate	1	
Colon+essential thrombocytemia	1	
Kidney+rectum	1	
Colon+uterus	1	

TABLE 3. Postoperative Complications Most Frequent in the Groups Compared

Complication	Group A, No. (%)	Group B, No. (%)	Group C, No. (%)
Low cardiac output	6 (18)	6 (10.7)	11 (6.6)
Atrial fibrillation	2 (6)	5 (8.9)	15 (9)
Kidney failure	1 (3)	5 (8.9)	7 (4.2)
Respiratory failure	0	2 (3.5)	5 (3)
Mediastinitis	0	1 (1.7)	2 (1.2)
Superficial infection of incision	0	1 (1.7)	4 (2.4)

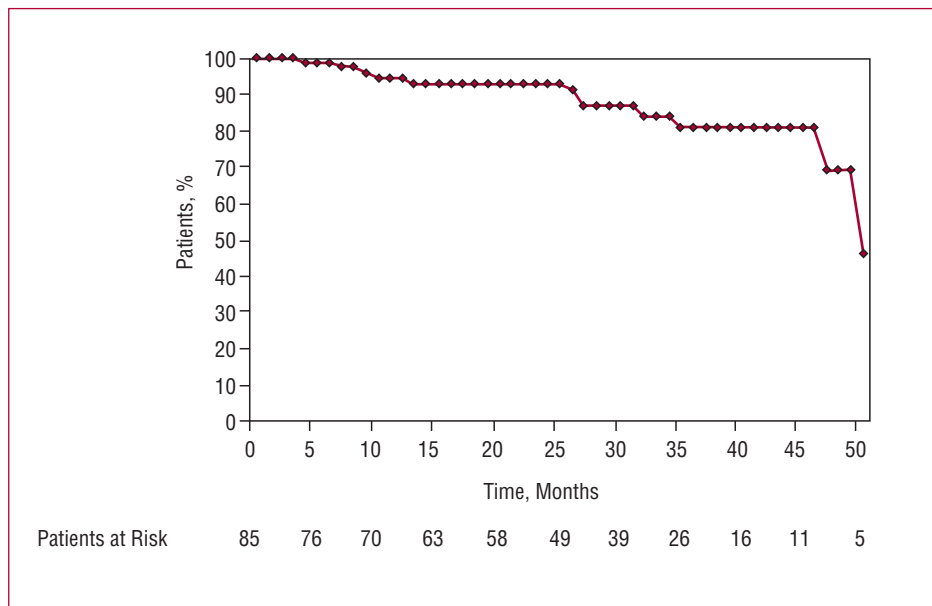


Figure 1. Actuarial survival of 89 patients affected by cancer, whether active or in complete remission, during follow-up after cardiac surgery with extracorporeal circulation.

(2.2% and 71.4%) that we did not find between groups B and C.

Survival during follow-up in groups A, B, and C is shown in Figure 2. In group C, only age ($P=0.0004$) was a risk factor for mortality in follow-up (hazard ratio [HR] = 1.19; 95% CI, 1.08-1.32). Risk factors for reduction of survival in patients with cancer appear in Table 4. No factor is significantly associated with tumor recurrence.

In the group of patients affected by a tumor, the type of valvular prosthesis implanted (mechanical or bio-prosthesis) does not influence in-hospital mortality (6.1% and 0%) or during follow-up (13% and 17.4%) nor in the appearance of postoperative complications (30.4% and 32.6%), recurrence of cancer (21% and 21.4%), or the appearance of new tumors (4.8% and 0%).

The number of readmissions was significantly greater in patients with malignancy neoplastic disease (10.5%) (9.6% in group A and 11.1% in group B) than in group C (4.4%). Cause was cardiac in 42.8% of group C patients, whereas in groups A and B 87.5% of the readmissions were due to the tumor or complications derived from it.

DISCUSSION

Controversy about the suitability of cardiac surgery in patients with cancer, especially if they are not in complete remission, is increasing frequent in daily clinical practice. As no objective reasons exist to justify the greater mortality in these patients, the interest of the procedure centers on perspectives for long-term survival and the risks due to ECC⁶ use through direct alteration of the immune system,^{1,7-9} can exacerbate the tumor and favor dissemination¹⁰ and/or recurrence.

Since the 1990s, studies about cancer patients undergoing cardiac surgery have been published.^{1,2,6,7,11} Some exclude recently diagnosed or untreated¹ cancers and others refer exclusively to the association of cardiac surgery and the simultaneous or deferred surgical excision of pulmonary tumors.^{4,7,8} A third group describes the results of surgical treatment of cancers that affect the heart as primary tumor or metastasis and that need ECC for resection.^{9,12} Finally, one last group includes patients affected by tumors with special characteristics such as hematologic malignancies.^{3,4,11} Publications are few and

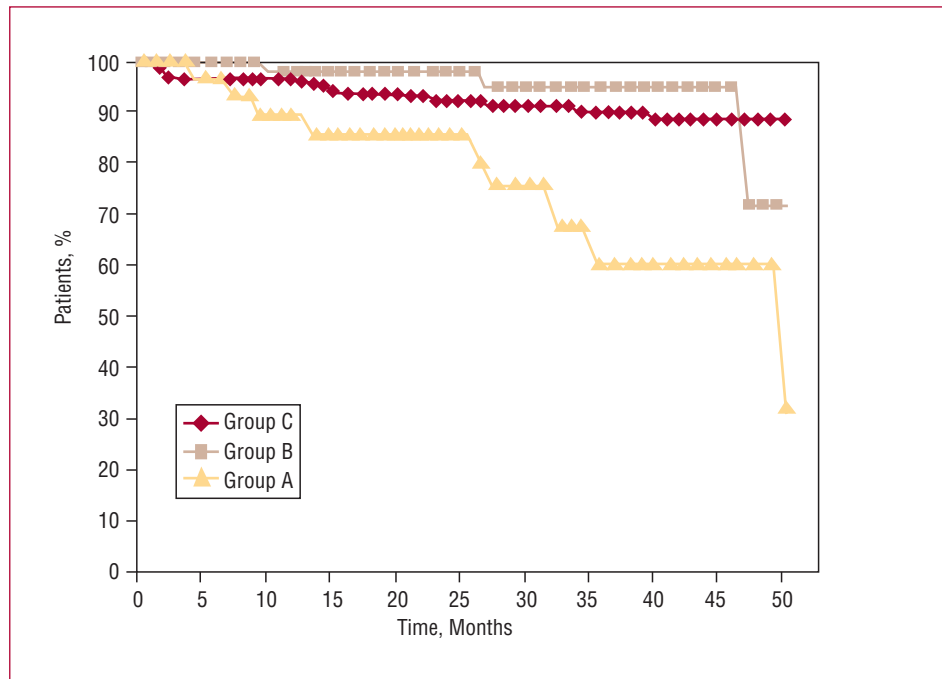


Figure 2. Actuarial survival after cardiac surgery with extracorporeal circulation as a function of the stage of the cancer (active in group A and in complete remission in group B) and comparison with the control population (group C).

TABLE 4. Risk Factors of Mortality During Follow-up in the Population With Cancer

Risk Factor	HR	95% CI	P
Preoperative left ventricular dysfunction	6.12	1.27-29.4	.023
Interval between cancer diagnosis and surgery <2 years	5.49	1.41-21.35	.013
Group A	4.45	1.18-16.76	.027
Chronic obstructive pulmonary disease	4.10	1.04-16.09	.042
Group B	1.18	0.63-2.21	.592

CI, confidence interval; HR indicates hazard ratio.

Details of the variables included to adjust the Cox proportional risk model appear in Methods, above. HR of group B was obtained taking as a reference the population of group C, composed of patients without known tumor operated with extracorporeal surgery.

far between and the series are limited and heterogeneous due to the low number of patients operated. It is difficult to avoid the risk of selection bias and, moreover, the different origins, stages, and degrees of differentiation and propagation of the tumors make the comparison of results difficult.

Our study group includes all patients affected by a neoplasia presenting over a 4-year period, after diagnosis of extension and survival estimation by an oncologist. Surgery was accepted only if the estimated prognosis of survival time in cancer patient was greater than the estimated for the cardiomyopathy that conditioned indication for surgery. Patients with metastasis did not undergo surgery. In 6 patients, diagnosis of the tumor and cardiac disease was almost simultaneous so surgery was performed prior to treating the cancer. In no patient were cardiac surgery and excision of the tumor performed during the same intervention.

The number of patients with isolated cardiac surgery is low (17% vs 34% in the general population in our

area). This may be due to a selection bias, inevitable on our part, as only patients with clinical angina non eligible for percutaneous treatment thru angioplasty-stent are referred for surgical intervention. Therefore, the low number of patients operated without ECC (2 patients) prevents us from comparing morbidity and mortality, survival, and tumor recurrence with patients operated with ECC^{13,14} consequently they have been excluded from the study.

In-hospital mortality (4.5%) is comparable with that of other series (4.1%-17%),^{1,3-6} similar to that expected according to the Euroscore scale and in no case a consequence of the tumor. Thus, neither in patients with malignancies in treatment or recently diagnosed can this be used as an excuse to exclude them from surgery.

With regard to morbidity, no postoperative complication seems significantly linked to cancer, whether active or in complete remission. Hematologic malignancies constitute a special group of tumors associated with greater mortality and incidence of hemorrhagic

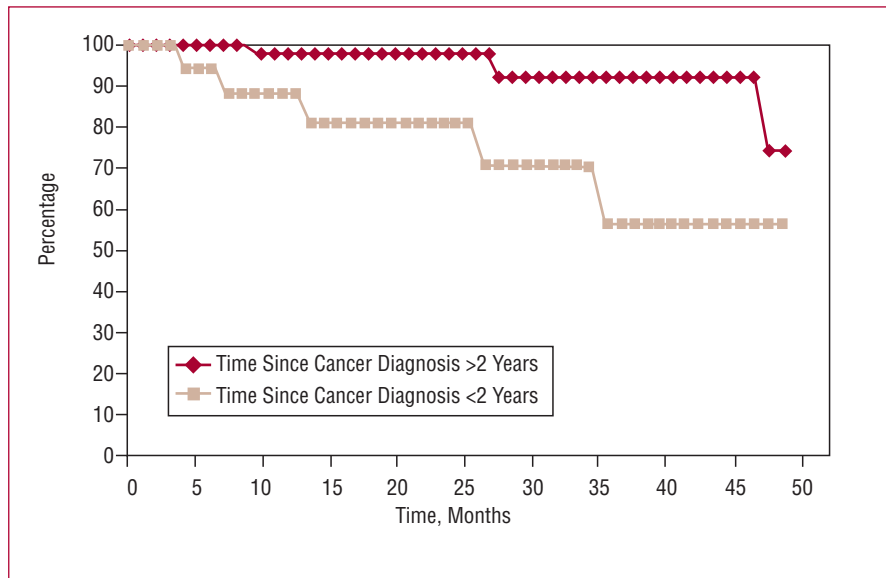


Figure 3. Survival of the patients with cancer (groups A and B) as a function of the interval between cancer diagnosis and cardiac surgery with extracorporeal circulation. Survival is reduced in patients with an interval <2 years.

complications,^{1,3,4,11} infections, and mediastinitis after ECC.²⁻⁴ In these patients, various authors advise careful preoperative evaluation and the use of techniques without ECC or valve bioprostheses. The 10 patients affected in our series by hematopathy did not present greater mortality or incidence of infectious, or hemorrhagic complications.

As in other series,^{1-3,6} long-term survival is directly related, firstly, with the cancer (which caused 8 deaths) and secondly with the cardiomyopathy, especially in patients with preoperative left ventricular dysfunction (3 deaths). Although survival is significantly reduced in patients with active cancer (group A), the distance between the curves in Figure 2 does not really become important until 24 months of follow-up, even when compared with survival in patients without known tumors (group C). Consequently, it seems inappropriate to exclude cardiac surgery in patients with cancer (even in the active phase) solely as a function of expected survival because, although less, results seem acceptable. As in other studies,⁶ survival falls if the interval between cancer diagnosis and surgery is <2 years (Figure 3). Although studies exist that indicate metastasis inhibits anticoagulant therapy.^{9,15} Furthermore, we have found no significant differences in risk of hemorrhage, survival, tumor recurrence, metastasis, and/or appearance of new tumors as a result of its use.

During follow-up, mortality of neoplastic etiology does not appear to be related with use of ECC, as only 1 of 8 deaths is identifiably due to tumor reactivation; the rest are due to the evolution of active cancers. Although the incidence of tumor recurrence in group A is double that in group B (33.3% and 15.5% respectively), in group B recurrent tumors are late and their timing is difficult to relate with immune system alterations associated with ECC. Similarly, readmissions are more frequent among patients affected by cancer, both for need for treatment

and the appearance of complications secondary to the tumor.

Limitations of the Study

As this study is retrospective with a limited number of patients, results should be interpreted with caution. Groups A and B are heterogeneous in origin, extension, and stages of the cancers and there is an uncontrollable selection bias that reduces the number of coronary patients by comparison with the general population in our area. This complicates the construction of a control group composed of patients operated without ECC to determine whether the technique is efficient in reducing recurrence and prolonging survival.

CONCLUSIONS

We have found no significant increase in morbidity and mortality of cardiac surgery with ECC in cancer patients, even in an active stage, by comparison with the normal population in our area.

It seems that the survival of cancer patients who undergo cardiac surgery is more closely related with the progression of the tumor than the surgical procedure. Medium-term survival is acceptable, although less in patients with an active cancer at the time of the intervention and in those with <2 years between cancer diagnosis and surgery. Rates of readmission are greater than in the general population and are principally due to need for treatment of the cancer and/or complications arising from it.

Individual evaluation of each case should consider both the tumor stage and chances of complete remission (even in active cancers) before discounting heart surgery.

Wider-ranging studies are needed to enable comparison of results of morbidity and mortality, and survival with and without the use of ECC to identify its influence on these variables and on long-term recurrence.

REFERENCES

1. Canver CC, Marrin CA, Pluma SK, Nugent WC. Should a patient with a treated cancer be offered an open heart operation? *Ann Thorac Surg.* 1993;55:1202-4.
2. Franchesca S, Frazier OH, Radovancevic B, de Caro LF, Reul G, Cooley D. Concomitant cardiac and pulmonary operations for lung cancer. *Tex Heart Inst J.* 1995;22:296-300.
3. Fecher AM, Birdas TJ, Haybron D, Papasavas PK, Evers D, Caushaj PF. Cardiac operations in patients with hematologic malignancies. *Eur J Cardiothorac Surg.* 2004;25:537-40.
4. Samuels LE, Kaufman MS, Morris RJ, Styler M, Brockman SK. Open heart surgery in patients with chronic lymphocytic leukaemia. *Leuk Res.* 1999;23:71-5.
5. Parsonnet V. Risk stratification in cardiac surgery: is it worthwhile? *J Card Surg.* 1995;10:690-8.
6. Mistiaen WP, van Cauwelaert P, Muylaert P, Wuyts F, Harrison F, Bortier H. Effect of prior malignancy on survival after cardiac surgery. *Ann Thorac Surg.* 2004;77:1593-7.
7. Davydov MI, Akchurin RS, Gerasimov SS, Polotsky BE, Stilidi IS, Machaladze ZA, et al. Simultaneous operations in thoraco-abdominal clinical oncology. *Eur J Cardiothorac Surg.* 2001;20:1020-4.
8. Danton MH, Anikin VA, McMagnus KG, McGuigan JA, Campalani G. Simultaneous cardiac surgery with pulmonary resection: presentation of series and review of literature. *Eur J Cardiothorac Surg.* 1998;13:667-72.
9. Zacharski LR, Constantini V, Wojtukiewicz MZ, Memoli VA, Kudryk BJ. Anticoagulants and cancer therapy. *Semin Oncol.* 1990;17:217-27.
10. Akchurin RS, Davidov MI, Partigulov SA, Brand JB, Shiriaev AA, Lepilin MG, et al. Cardiopulmonary bypass and cell-saver technique in combined oncologic and cardiovascular surgery. *Artif Organs.* 1997;21:763-5.
11. Christiansen S, Schmid C, Loher A, Scheld HH. Impact of malignant haematological disorders on cardiac surgery. *Cardiovasc Surg.* 2000;8:149-52.
12. Vaporciyan AA, Rice D, Correa AM, Walsh G, Putnam JB, Swisher S, et al. Resection of advanced thoracic malignancies requiring cardiopulmonary bypass. *Eur J Cardiothorac Surg.* 2002;22:47-52.
13. Nurözler F, Kutlu T, Küçük G. Off-pump coronary bypass for patients with concomitant malignancy. *Circ J.* 2006;70:1048-51.
14. Ochi M, Yamada K, Fujii M, Ohkubo N, Ogasawara H, Tanaka S. Role of off-pump coronary artery bypass grafting in patients with malignant neoplastic disease. *Jpn Circ J.* 2000;64:13-7.
15. Francis JL, Amirhosravi A. Effect of antihemostatic agents on experimental tumor dissemination. *Semin Thromb Hemost.* 2002;28:29-38.