ORIGINAL ARTICLE

Pre-operative cardiac risk stratification for noncardiac surgery in cancer patients using myocardial perfusion scintigraphy

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ABSTRACT

Background: Cancer patients are at a higher risk for any cardiac event during and post surgery, due to an altered coagulation state and anemia, and can have additive effect if the patient had previous history of any cardiac event or risk factor for coronary artery disease such as hypertension and diabetes.

Methods: 100 consecutive patients, who were being planned for the oncological surgery, were enrolled in this study for preoperative gated myocardial perfusion scintigraphy using99mTcsestamibi with adenosine stress. After acquiring the data, MPI were reconstructed and analyzed using visual assessment as well as QPS program and summed stress score (SSS) was obtained. Based on visual assessment and SSS, we divided patients into low- and high-risk groups.

Results: 100 patients (57 female and 43 male) with a mean age 61.25 years. 63% had a history of diabetes,73% hypertension, 34% were known smokers while 42% had a family history of coronary artery disease and 15 patients has CAD. 61% fell into the low-risk group and 39%in the high-risk group. In the low-risk group 1 patient needed inotropic support post operatively while in high-risk group, 6 patients had cardiac events postoperatively. Subset analysis of these showed; 3 (7.69%) had an episode of angina prior to discharge, 2 died with cardiac-arrest due to myocardial infraction and 1 needed inotropic support postoperatively and surgery was deferred in 4 patients due to their very low LVEF and high SSS. These 4 patients were further evaluated by cardiologist for future management.

Conclusion: In low-risk group patients, stress MPI has a high negative predictive value for peri- and post operative cardiac events in cancer patients. While patients with cancer and labeled as high-risk on myocardial perfusion imaging, whether demonstrating scar or ischemia, should prompt appropriate peri- and post operative management to minimize major cardiac events.

Keywords: Myocardial perfusionscintigraphy, Pre-operative risk assessment,^{99m}Tc-sestamibi, Pharmacological stress,Adenosine, Coronary artery disease

INTRODUCTION

Coronary artery disease (CAD) is the leadingcause of death with no limitation to geographicboundaries accounting for about 16.7 milliondeaths worldwide [1]. Cancer by itself isassociated with coagulation disorders due tohypercoagulable state and can cause coronarythromboemboli. However, there is no definiteevidence that cancer by itself or any particulartumour type predisposes to coronaryatherosclerosis [2]. No single test candiagnose or stratify the risk of having CAD.The evidence that myocardial perfusionimaging(MPI), has a strong prognostic value,is overwhelming [3] because of its higherdiagnostic sensitivity and specificity thanexercise electrocardiography (80% and 92%vs. 64% and 82% respectively) for coronaryartery disease [4]. MPI is also used forassessing the functional importance of knowncoronary stenoses risk stratification beforemajor non-cardiac surgery [5].

Gated stress MPS is the most commonly usedand well documented noninvasive method forrisk stratification. It is most cost-effective inpatients with a clinically intermediate risk ofa subsequent cardiac event [6]. According toACC/AHA 2007 Guidelines on perioperativecardiovascular evaluation and care for noncardiacsurgery in patients with known CADor the new onset of signs or symptomssuggestive of CAD, baseline cardiacassessment should be performed [7].

The surgery-specific cardiac risk of noncardiacsurgery is related to two importantfactors. First, the type of surgery by itself, andsecond, the likelihood of underlying heartdisease. Pharmacologic testing with MIBISPECT has been used to assess risk of futurecardiac events in patients in a stable conditionunable to perform an exercise test. Anabnormal

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MIBI study is reported to be thestrongest independent predictor of increasedrisk of nonfatal MI or cardiac death (oddsratio, 10.0; 95% CI, 2.3 to 43.0) [8]. Severalstudies have assessed the perioperative andlong-term prognostic value of dipyridamoleMIBI imaging in vascular surgery patients. Literature review suggests that dipyridamole,adenosine, and dobutamine testing with MIBIimaging may be effective for perioperative andlong-term risk stratification in some patientsundergoing non-cardiac surgery [9]. However,more studies are needed to better definewhich patients may benefit from testing basedon clinical risk factors and type of surgery etc.The purpose of this study was to evaluate theusefulness of gated myocardial perfusionscintigraphy (G-SPECT) with Adenosinepharmacological stress for determining thefrequency of cardiac event associated withnon-cardiac surgery in cancer patients.

METHODS

We conducted a cross sectional observationalstudy at our department. We included 100 cancer patients fulfilling the inclusion criteria (Table 1), who were referred from themedicine and anesthesia departments of SKMCH & RC for preoperative cardiac riskstratification. The patients were advised tofast for 4 hours, with no caffeine for at least12 hours prior to study. After giving informedconsent, the patients underwent gatedmyocardial perfusion scintigraphy prior tosurgery as two-day protocol. On the first day,stress myocardial scintigraphy was performedusing adenosine infused over 6 minutes in adose of 140 µg per kg body weight per minutefor pharmacological stress. ^{99m}Technetium-2-methoxyisobutylisonitrile (^{99m}Tc-sestamibi)was injected 3 minutes after starting theadenosine infusion. Patient was advised totake fatty meal at 20 minutes post injectionand gated single-photon emission computedtomography (G-SPECT) was performed 45-60minutes postinjection by using a dual-headedgamma camera with SPECT capability. Imageswere obtained by using low-energy high-resolution collimators. Energy window 20% was centered at 140 keV with matrix size of 64 X 64.

SPECT was obtained by step and shootmethod, 1800 of motion arc, 450 right anterioroblique (RAO) to 135o left posterior oblique(LPO) with 32 projections, each of 30-secondduration per projection, 8 frame perprojection. Gated SPECT was obtained by ECGsynchronized data collection. Images werereconstructed by using QPS/QGS software.

Stress and rest scan images was sliced intothree planes: short axis (SA), horizontal longaxis (HLA) and vertical long axis (VLA). Polarmap (bull's eye) was used for quantitativeperfusion defects analysis and 20-segmentsummed stress score (SSS) was calculated.

If there was evidence of a perfusion defect instress scintigraphy, the patient was called infor rest scintigraphy the next day. Both thestress and the rest images were processedtogether to see evidence of reperfusion. Postscintigraphy risk stratification was mentionedin the report on the basis of 20-segmentsummed stress score (SSS).

The patient was followed up and observed forany cardiac related event (e.g., cardiac death,myocardial

Table 1. Inclusion and exclusion criteria

Inclusion Criteria 1. Advance age of more than 40 years 2. Either sex (male and female) In addition, one or more than one of the following: • Abnormal ECG (Left ventricular hypertrophy, LBBB, ST abnormalities) • Rhythm other than sinus (e.g. atrial fibrillation) • Low functional capacity (e.g. inability to climb one flight of stairs) • History of stroke • Known case of systemic hypertension and on medication • Mild angina pectoris (Canadian class I or II) • Prior myocardial infarction by history or pathological Q waves • Compensated or prior congestive heart failure • Known case of diabetes mellitus • Unstable coronary syndrome including acute myocardial infarction • Unstable or severe angina (Canadian class III or IV) • Decompensate congestive heart failure
Exclusion Criteria: 1. Previous history of surgery 2. Post chemotherapy 3. Pregnancy 4. High grade atrioventricular block 5. Symptomatic ventricular arrhythmias 6. Supraventricular arrhythmias 7. Severe valvular disease

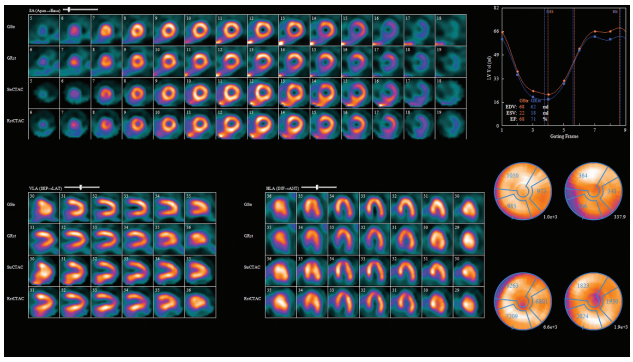

Figure 1 Normal myocardial perfusion scan (SSS = 0).

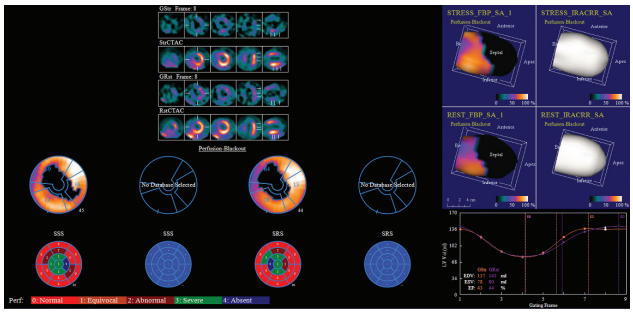

Figure 2 Anteroapaical wall infraction extending into inferior wall.

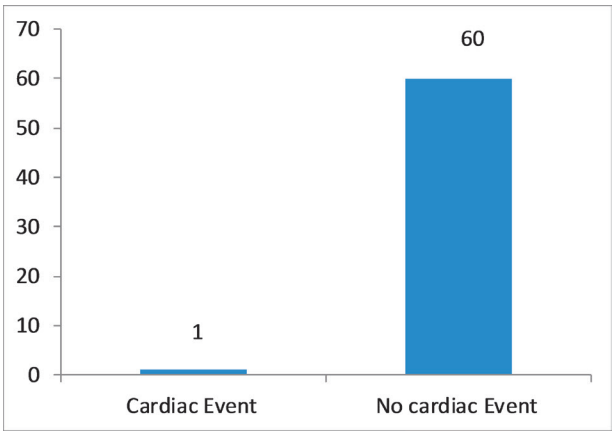

Figure 3 Frequency of cardiac events in low risk group

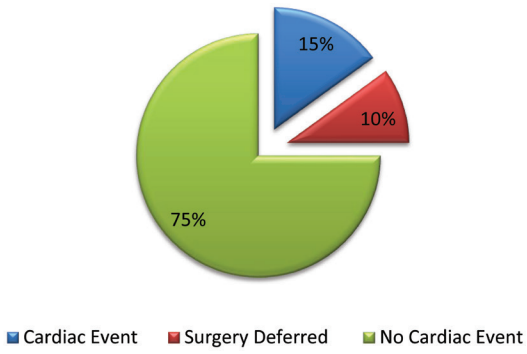

Figure 4 Frequency of cardiac events in low risk group

ischaemia, heart failure, fatalarrhythmia, unstable angina, etc.) peri andpost operatively up to 2 weeks, and thesewere documented.

Statistical Analysis

The data analysis was carried out usingcomputer based Statistical Package for SocialSciences (SPSS) version 14. Quantitativevariables such as age and qualitative variablessuch as sex (male/female), diabetes,hypertension, body mass index, LVEF > 55%and final conclusion, i.e. per-operative cardiacevent (Yes/No) and post-operative cardiacevent (Yes/No) was presented by calculatingthe frequency and percentage. Correlation ofany cardiac event (peri- and post-operatively)was made with the post-scintigraphic riskstratification.

RESULTS

Out of 100 patients, 43 were male and 57female with ages ranging from 41-88 years with a the mean age of 61.25 years. Thirty eight patients were operated on for breastcancer, 10 for colon cancer, 8 for lung cancer,6 stomach cancer, 5 for oesophageal cancer,5 for renal cell carcinoma (RCC), 4 for hepatocellular cancer (HCC), and 24 for other cancers which included cervical, ovarian, tongue, pancreatic and thyroid cancers.

Sixty-three percent of that patients had a history of diabetes, 73% were hypertensive,34% were known smokers whilst 42% had family history of coronary artery disease and15% patients has CAD, 59% had body mass index (BMI) more than 25 while 41% had BMI less than 25.

Following data acquistion, QPS software was used for quantitative analysis including calculation of summed stress score (SSS). Out of total 100 patients, 61 had a SSS ≤ 4 (Figure1), which was considered as normal while 39had SSS ≥ 5 (Figure 2). On subset analysis of these 39 patients, 15 had SSS between 5-8,which was considered as mildly abnormal, 20 patient had SSS between 9-13 which was considered as moderately abnormal and 4patients had SSS more than 13 which was considered as severely abnormal. On the same stress MPI, QGS software was used to calculate the left ventricular ejection fraction (LVEF). Minimum LVEF was 22% and maximum LVEF was 87%. 18 out of 100patients had LVEF less than 55%. On the basis of SSS and LVEF out of 100, 39 patients fell into high-risk group for peri- and post- operative cardiac events while 61 patients were assigned in to the low-risk group for cardiac events. On subset analysis of low-risk group, only one patient out of 61 patients (1.63%) needed inotropic support postoperatively (Figure 3). This patient had SSS of 3 and a LVEF 49% on MPI. The patient was a 73-year-old male with risk factors for CAD including diabetes, hypertension, smoking with

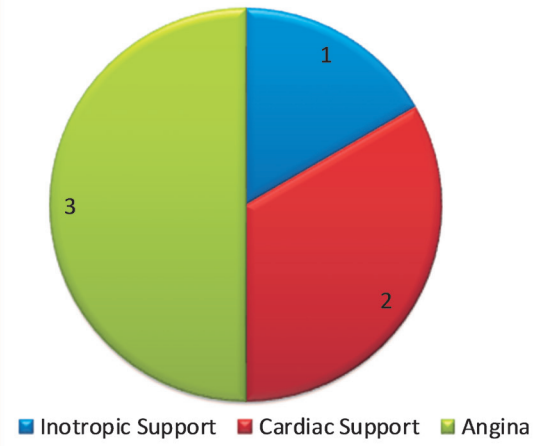

Figure 5 Frequency of cardiac event in high risk patients

positive family history for CAD but no previous history of CAD.

In the high-risk group, 6 (15%) patients had adverse cardiac events postoperatively and surgery was deferred in 4 (10%) patients(Figure 4). Subset-analysis of these showed:3 (7.69%) had an episode of angina prior to discharge, 2 (5.12%) died with cardiac-arrest and 1 (2.56%) needed inotropic supportpost-operatively (Figure 5). Four patients inwhom surgery deferred were further revaluated by cardiologists for future management. All of these 4 patients fell into moderately to severely abnormal category according to their SSS; out of these, one patient had an SSS in the range of 9-13 whilst the rest of the 3 patients has SSS more than 13. All these patients also had a very low LVEF at 22%, 26%, 46% and 29% respectively. On visual analysis these 4 patients has moderate to large size fixed perfusion defects indicating old myocardial infarction.

DISCUSSION

Patients undergoing major non-cardiac surgery have a significant risk of cardiovascular morbidity and mortality [10]. Although the peri- and post-operative event rate has declined over the past 30 years as a consequence of recent developments in the anaesthesiology and surgical techniques (e.g., regional anaesthesia and endovascular treatment modalities), peri- and postoperative cardiac complications remain a significant problem. A pooled analysis of several large studies found a 30-day incidence of cardiac events (peri- and post-operative myocardial infarction or cardiac death) of 2.5% in unselected patients over the age of 40 years [11, 15]. These complications were higher in vascular surgery patients, who had an incidence of 6.2% for cardiac events [12]. The risk of peri- and post-operative cardiac complications is the summation of the individual patient's risk and cardiac stress related to the surgical procedure.

The first step in pre-operative care is an adequate identification of patients at risk for peri- and post-operative cardiac events. In the past decades, several risk indices have been developed in this context to stratify surgical patients including introduction of Bayesian approach using pre-test probabilities in 1986, which was later modified by Lee et al. in 1999 [13]. This Revised Cardiac Risk Index, is currently the most widely used model of risk assessment in non-cardiac surgery. This index identifies 6 predictors of major cardiac complications including: 1) high-risk surgery, 2) ischaemic heart disease, 3) congestive heart failure, 4) cerebrovascular disease, 5) insulin-dependent diabetes mellitus, and 6) renal failure.

When the pre-operative risk assessment indicates an increased cardiac peri- or postoperative risk, further cardiac testing is warranted [13]. The predominant theme of testing is the impact of test results on periand post-operative management: if test results will not influence management, testing is not recommended. According to the 2007 guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA), patients with active cardiac conditions (i.e., unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease) have to be evaluated and treated before surgery [14]. Pre-operative cardiac testing for elective surgery is reasonable for patients with intermediate to high clinical risk factors and poor functional capacity who require vascular surgery. Pre-operative testing may be considered in patients with at least 1 to 2 or more clinically known risk factors and poor functional capacity undergoing for non-cardiac surgery [15].

Noninvasive testing is not recommended for patients without clinical risk factors undergoing intermediate or low-risk noncardiac surgery. Several noninvasive tests are available for peri- and post-operative risk assessment. The most commonly used stress test for detecting myocardial ischaemia is the treadmill or cycle ergometer test. These tests provide an estimate of the functional capacity and haemodynamic response and detect myocardial ischaemia by ST-segment changes. The accuracy varies widely among studies [16]. However, an important limitation in patients undergoing non-cardiac surgery is the frequently limited exercise capacity in the elderly and the presence of claudication, arthritis, or chronic obstructive pulmonary disease. Consequently, non-physiologic stress tests, such as dobutamine stress echocardiography or dipyridamole or adenosine myocardial perfusion scintigraphy (MPS), are recommended in patients with limited exercise capacity [17, 24].

Myocardial perfusion scintigraphy is a widely used imaging technique for pre-operative evaluation. This technique involves intra venous administration of a small quantity of a radioactive tracer such as a technetium-99m labelled radiopharmaceutical. Images are

obtained at rest and during vasodilator stress [18]. Detection of CAD is based on a difference in blood flow distribution during vasodilator stress induced by insufficient coronary blood flow increment attributed to coronary stenosis. A positive MPS is associated with increased risk of peri- and post-operative cardiac complications. Studies indicate that MPS is highly sensitive for prediction of cardiac complications, but the specificity has been reported to be less satisfactory [19, 23].

From the results of our study, those patients who have intermediate to high pre-test probability for CAD, are considered the best candidates for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI). In patients with normal stress ^{99m}Tc-sestamibi SPECT, MPI is associated with a very low risk of a cardiac event, as in our study it is only 1.63% while in literature it is 0.6% annually [20, 25].

Patients in the high-risk group according to summed stress score on MPI were further divided into 3 groups including mildly abnormal, moderately abnormal and severely abnormal risk groups. Surgery was deferred in all 4 patients who fall in severely abnormal group according to SSS and lower than the normal LVEF, and these patients were referred to a cardiologist for further evaluation and treatment according to the guidelines. Amongst the patients in the sub group of mild to moderately abnormal SSS on MPI, a cardiac event occurred in 6 (15.38%) patients only. Two (5.12%) patients had death due to myocardial infraction (MI) while 3(7.69%) had episode of chest pain without a rise in troponin I though this percentage of cardiac event is slightly higher than what the literature quotes, i.e about 6% (21,22) but we should not forget that all of these 6 patients were high-risk cancer patients with multiple known risk factors for CAD and all of them underwent high-risk non-cardiac surgery. This kind of surgery by itself carries a high mortality and morbidity per operatively due to prolonged anesthesia and surgery time and postoperatively due to prolonged bed rest.

Our study has some limitations including: 1) small sample size, 2) sampling is nonprobability; purposive so the results cannot be generalized and does not represent the entire cancer population; and 3) ideally Summed Rest Score (SRS) and Summed Difference Score (SDS) should also be calculated on the rest perfusion imaging in those patients in whom the stress MPI turned out to be abnormal.

CONCLUSION

Stress MPI provides incremental diagnostic and prognostic value in patients at an intermediate or high pretest likelihood of CAD or patients with known risk factors for CAD. Patients who exhibit normal myocardial perfusion and function or have a small defect with normal left ventricular function have less likelihood of any adverse cardiac event periand post-operatively; however, patients with cancer and labelled as high-risk on myocardial perfusion imaging, whether demonstrating scar or ischaemia, should have prompt and appropriate peri- and post-operative management to minimize major cardiac events.

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List of abbreviation

CAD	Coronary artery disease
(G-SPECT)	Gated single photon emission computed tomography
HLA	Horizontal long axis
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MPS	Myocardial Perfusion study
(SA)	Short axis
SSS	Summed stress score
SRS	Summed Rest Score
SDS	Summed Difference Score
VLA	Vertical long axis

Conflict of Interests

None

Ethical approval

The study was approved by the CPSP research and evaluation cell including ethical consideration.

Consent for publication from the study subjects

Written informed consent was taken from all the participants.

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