Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209

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Background: This study aimed to determine the clinical benefit of neoadjuvant methotrexate, doxorubicin, vinblastine, and cisplatin (MVAC) in patients with muscle-invasive bladder cancer (MIBC) treated with radical cystectomy.

Patients and methods: Patients with MIBC (T2-4aN0M0) were randomised to receive two cycles of neoadjuvant MVAC followed by radical cystectomy (NAC arm) or radical cystectomy alone (RC arm). The primary end point was overall survival (OS). Secondary end points were progression-free survival, surgery-related complications, adverse events during chemotherapy, proportion with no residual tumour in the cystectomy specimens, and quality of life. To detect an improvement in 5-year OS from 45% in the RC arm to 57% in the NAC arm with 80% power, 176 events were required per arm.

Results: Patients (N = 130) were randomly assigned to the RC arm (N = 66) and the NAC arm (N = 64). The patient registration was terminated before reaching the initially planned number of patients because of slow accrual. At the second interim analysis just after the early stoppage of patient accrual, the Data and Safety Monitoring Committee recommended early publication of the results because the trial did not have enough power to draw a confirmatory conclusion. OS of the NAC arm was better than that of the RC arm, although the difference was not statistically significant [hazard ratio 0.65, multiplicity adjusted 99.99% confidence interval 0.19–2.18, one-sided P = 0.07]. In the NAC arm and the RC arm, 34% and 9% of the patients had pT0, respectively (P < 0.01). In subgroup analyses, OS in almost all subgroups was in favour of NAC.

Conclusions: This trial showed a significantly increased pT0 proportion and favourable OS of patients who received neoadjuvant MVAC. NAC with MVAC can still be considered promising as a standard treatment.

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introduction

Radical cystectomy has been the gold standard for treatment of muscle-invasive bladder cancer (MIBC) for the last three decades. Although radical cystectomy provides excellent local control, survival is associated with the pathological tumour stage of the cystectomy specimen. Five-year overall survival (OS) estimates range from 81% to 93% for patients with pT0/a/isa/1 disease to from 46% to 48% for patients with pT3 disease [1–3].

Neoadjuvant chemotherapy (NAC) offers potential advantages in tumour downstaging and eradication of micrometastases. The Southwest Oncology Group (SWOG)-8710 trial, which randomised patients with stage T2–T4a bladder cancer to receive either radical cystectomy alone or three cycles of MVAC followed by cystectomy, demonstrated a survival benefit for patients receiving neoadjuvant MVAC with a 5-year OS of 57% compared with 43% for patients undergoing cystectomy alone (two-sided \( P = 0.06 \)) [4]. The Medical Research Council (MRC) carried out another randomised phase III trial of either no NAC or three cycles of cisplatin, methotrexate, and vinblastine (CMV) in patients with MIBC treated by cystectomy and/or radiotherapy [5]. The MRC study showed a 16% reduction in the risk of death after neoadjuvant CMV [hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.72–0.99, \( P = 0.037 \)] [5].

Before these trials, several studies failed to prove the survival benefit of NAC [6, 7]. Although meta-analyses including those negative trials concluded that cisplatin-based NAC for patients with MIBC provided a 5%–7% OS advantage [8, 9], NAC is not common in either the United States [10] or European countries [11]. This may mean that evidence from past positive studies [4, 5] has had little impact on physicians’ decisions to perform NAC, although other factors, e.g. a low incidence of referrals by urologists for chemotherapy, confidence in salvage chemotherapy as an equivalent alternative [10], concern for patients’ comorbidities, including renal insufficiency, etc., may also be involved.

To confirm the benefit of neoadjuvant MVAC for OS, we conducted a randomised phase III trial for patients with clinical T2–T4aN0M0 bladder cancer who were candidates for radical cystectomy.

patients and methods

study design and inclusion criteria

Patients with muscle-invasive urothelial carcinoma (UC) of the bladder were randomly assigned to a group with NAC followed by surgery or one with surgery alone (Figure 1). Randomisation was carried out with a minimisation method according to the institution, and clinical T stage.

Study inclusion criteria were T2-4aN0M0; within 8 weeks from transurethral resection of the bladder tumour (TURBT); histologically proven UC [UC histology must be dominant (>50%)]; no prior or concomitant UC other than non-MIBC; no prior chemotherapy or radiation therapy; age 20–75 years old; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; adequate organ function [white blood cell count ≥4000 cells/mm\(^3\) or neutrophil count ≥2000 cells/mm\(^3\), platelets ≥100 000 cells/mm\(^3\), serum creatinine ≤1.5 mg/dl, total bilirubin ≤1.5 mg/dl, aspartate transaminase ≤2.5 × upper limit of normal (ULN), alanine transaminase ≤2.5 × ULN]. The diagnosis of TNM stage required: (i) pathological stage ≥T2 in the TURBT specimen, and (ii) no lymphatic or distant metastasis on computed tomography (CT) or magnetic resonance imaging (MRI). The protocol was reviewed and approved by the Japanese Clinical Oncology Group (JCOG) Protocol Review Committee on January 2002 and by the institutional review boards of the participating institutions. All patients provided written informed consent.

treatment plan

Chemotherapy started within 28 days of randomisation and consisted of two cycles of MVAC that comprised methotrexate 30 mg/m\(^2\) i.v. on days 1, 15,
and 22, vinblastine 3 mg/m² i.v. on days 2, 15, and 22, doxorubicin 30 mg/m² i.v. on day 2, and cisplatin 70 mg/m² i.v. on day 2. Treatment cycles were repeated every 28 days.

Radical cystectomy with bilateral pelvic lymphadenectomy including the external iliac, internal iliac, and obturator nodes was carried out within 28 days after randomisation in patients assigned to surgery alone, and within 28 days following the last dose of chemotherapy in patients receiving NAC. For urinary reconstruction, a ureterocutaneostomy, ileal conduit, continent reservoir, or orthotopic neobladder was selected.

**assessment and follow-up**

Adverse events (AEs) were reported using the National Cancer Institute Common Toxicity Criteria grading version 2.0 (NCI-CTC v2.0). For patients receiving NAC, toxicity assessment, blood count, and blood chemistry were carried out every week during the chemotherapy. Intraoperative and post-operative complications were documented using the NCI-CTC v2.0 and the JCOG surgical morbidity criteria [12].

Patients were examined using CT or MRI at 6, 12, 18, 24, 36, 48, and 60 months after operation. Other investigations at each visit included a toxicity assessment, blood count, blood chemistry, and chest X-ray.

**end points and sample size**

The primary end point of this trial was OS. It was designed to detect an improvement in 5-year OS from 45% in the radical cystectomy alone (RC arm) to 57% in the neoadjuvant arm (NAC arm) with a power of 80% at the one-sided significance level of 5%. To observe the survival benefit in the projected 3 years of accrual and 5 years of follow-up, it was estimated that 176 patients would be required per arm. Thus, the planned sample size was set at 360 patients in total. Due to slow accrual, the protocol was amended to continue the patient accrual until either 6 years after the accrual start or until 150 patients could be enrolled. Secondary end points were progression-free survival (PFS), surgery-related complications, AEs during chemotherapy, proportion with no residual tumour (pT0) in the cystectomy specimens and quality of life.

**statistical analysis**

OS was calculated from randomisation to the date of death from any cause and was censored at the date of the last follow-up for surviving patients. PFS was calculated from randomisation to the date of documented progression or death (in the absence of progression) and was censored at the last date without any events. The primary end point of OS was analysed for all eligible patients by the stratified log-rank test with clinical T stages as strata, and stratified Cox regression analysis was carried out to estimate HRs stratified with the clinical T stage. PFS was analysed using the log-rank test and Cox regression analysis was carried out to estimate HRs. OS and PFS were estimated using the Kaplan–Meier method. The proportions with pT0 were compared using Fisher’s exact test. All P-values were two-sided unless otherwise specified. All statistical analyses were carried out using SAS 9.2 (SAS Institute, Inc.).

Initially, interim analyses were planned twice: the time after about two-thirds of patients were enrolled and the time after patient accrual was completed. However, the times were revised to about 5 years after the accrual start and the time after patient accrual completion because of the slow patient accrual.

This trial is registered with the UMIN Clinical Trials Registry, number C000000093.

**quality of life**

Quality of life was assessed by the Japanese edition of a bladder cancer-specific questionnaire, the Functional Assessment of Cancer Therapy–Bladder (FACT–BL), before treatment, after chemotherapy (only for the NAC arm), 6–8 weeks after cystectomy, and 1 year after randomisation. These data will be reported elsewhere.

**results**

**patients**

Between March 2003 and March 2009, 130 patients from 28 institutions in Japan were enrolled. The patient registration was terminated early because of slow accrual. Of the 130 patients enrolled, 64 were randomly assigned to the NAC arm and 66 to the RC arm. The Data and Safety Monitoring Committee (DSMC) recommended early publication at the second planned interim analysis in September 2012. This recommendation was mainly based on the judgment that it would be difficult to reach a confirmatory conclusion even at the final analysis in terms of the primary end point because of insufficient sample size. The patients’ characteristics are detailed in Table 1.

**chemotherapy**

Within the NAC arm, 56 patients received chemotherapy. The reasons why eight patients did not receive chemotherapy were patient refusal (N = 6), secondary cancer found after randomisation (N = 1) and severe cardiovascular disease just after being randomly assigned (N = 1). Of the 56 patients who received chemotherapy in the NAC arm, 54 (96%) completed two cycles of MVAC. The median total doses given were 239 mg (range 50–360) for methotrexate, 23 mg (range 5–36) for vinblastine, 100 mg (range 49–120) for doxorubicin, and 231 mg (range 114–282) for cisplatin.

The most commonly reported grade 3–4 event was neutropenia. Non-haematological toxicities were less common. There was no treatment-related death during the chemotherapy. Supplementary Table S1, available at Annals of Oncology online, summarises AEs during the neoadjuvant MVAC. No patients had a delay in cystectomy due to these AEs.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RC arm (N = 66)</th>
<th>NAC arm (N = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Range</td>
<td>35–74</td>
<td>40–75</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Clinical T stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>T3</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>T4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

RC, radical cystectomy; NAC, neoadjuvant chemotherapy; ECOG, Eastern Cooperative Oncology Group.
surgery and complications

The planned cystectomy was carried out in 59 and 65 patients in the NAC and RC arms, respectively. There was no significant difference in the operative time, estimated blood loss, proportion of transfusions, number of lymph nodes removed, and intraoperative complications between the arms (Table 2).

Of the early complications, no significant differences in the incidences of ileus, postoperative haemorrhage, wound infection, anastomotic stricture, neuropathy, thrombosis, postoperative pneumonia, febrile infection, or treatment of postoperative complications were observed. The incidence of anastomotic leaks in the RC arm was 1.5%, whereas that in the NAC arm was 12.1% ($P = 0.026$). The incidences of leakage in the RC arm and NAC arm were 12.3% and 1.7%, respectively ($P = 0.035$). There were no significant differences in the incidences of any late complications (supplementary Table S2, available at Annals of Oncology online).

Table 2. Intraoperative variables and complications

<table>
<thead>
<tr>
<th></th>
<th>RC arm</th>
<th>NAC arm</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td></td>
<td></td>
<td>0.60 $^b$</td>
</tr>
<tr>
<td>Median</td>
<td>456</td>
<td>460</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>200–780</td>
<td>270–853</td>
<td></td>
</tr>
<tr>
<td>Estimated blood loss (ml)$^a$</td>
<td></td>
<td></td>
<td>0.99 $^b$</td>
</tr>
<tr>
<td>Median</td>
<td>1670</td>
<td>1590</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>330–4740</td>
<td>380–6180</td>
<td></td>
</tr>
<tr>
<td>Transfusion$^a$</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>10 (15.6%)</td>
<td>10 (16.9%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54 (84.4%)</td>
<td>49 (83.1%)</td>
<td></td>
</tr>
<tr>
<td>Number of lymph nodes removed$^a$</td>
<td></td>
<td></td>
<td>0.41 $^b$</td>
</tr>
<tr>
<td>Median</td>
<td>18</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–45</td>
<td>0–52</td>
<td></td>
</tr>
<tr>
<td>Urinary diversion/reconstruction$^a$</td>
<td></td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Ureterocutaneostomy</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ileal conduit</td>
<td>34</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Continent reservoir</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Orthotopic neobladder</td>
<td>26</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Intraoperative complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>19 (29.2%)</td>
<td>23 (39.0%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Grade $\geq$3</td>
<td>8 (12.3%)</td>
<td>7 (11.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Venous/arterial injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>6 (9.2%)</td>
<td>7 (11.9%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Grade $\geq$3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>–</td>
</tr>
</tbody>
</table>

$^a$No data available for one patient in the RC arm due to exploratory laparotomy.

$^b$Wilcoxon rank-sum test.

$^c$Fisher’s exact test.

efficacy outcomes

The proportions of pT0 in the RC arm and NAC arm were 9.4% and 34.4%, respectively ($P = 0.0011$, supplementary Table S3, available at Annals of Oncology online). In the 127 patients who underwent cystectomy, the pT0 proportions in clinical T2 and T3/T4 were 29.2% and 16.1%, respectively ($P = 0.09$). In 59 patients undergoing cystectomy in the NAC arm, the proportions of pT0 in clinical T2 and T3/T4 were 43.8% and 29.6%, respectively ($P = 0.27$). The proportions of pN0 in the RC arm and NAC arm were 65.6% and 79.7%, respectively ($P = 0.11$). There was no significant difference in the surgical margin-positive proportions between the two arms.

The median follow-up for all randomised patients was 55 months. The HR for comparing NAC followed by cystectomy versus cystectomy alone for OS was 0.65 (multiplicity adjusted 99.99% CI 0.19–2.18, one-sided $P = 0.07$). The 5-year survivals were 62.4% (95% CI 49.0–73.2) and 72.3% (95% CI 59.2–81.9) in the RC and NAC arms, respectively (Figure 2A). Median OS was 82 months (95% CI 47–unreached) in the RC arm versus 102 months (95% CI 102–unreached) in the NAC arm.

At the time of this analysis, disease progression had occurred in 29 patients (45.3%) in the RC arm and 23 patients (35.9%) in the NAC arm. PFS had a tendency to be better in the NAC arm (HR 0.64, 95% CI 0.37–1.11, one-sided $P = 0.054$, Figure 2B). The 5-year PFS rates were 56.4% (95% CI 43.2–67.7) for the RC arm and 67.9% (95% CI 54.8–78.0) for the NAC arm. Median PFS was 78 months (95% CI 19–unreached) in the RC arm versus 99 months (95% CI 77–unreached) in the NAC arm.

Additional subgroup analyses of OS based on sex, age, clinical T stage, tumour morphology, number of tumours, tumour size, and histological grade showed a consistent advantage with NAC (supplementary Figure S1, available at Annals of Oncology online).

discussion

This randomised phase III study was conducted to detect the possible benefit for 5-year OS of two cycles of MVAC followed by radical cystectomy over cystectomy alone. In the final analysis, OS was better in the NAC arm, but the difference was not statistically significant. This was mainly because the small number of patients due to slow accrual resulted in low power to demonstrate the targeted benefit. The PFS of the NAC arm was longer than that of the RC arm, suggesting that two cycles of MVAC followed by cystectomy had more powerful therapeutic potential than cystectomy alone.

There were several reasons for the poor accrual of the patients in this multi-institutional study. The poor accrual might have been caused by lack of patients’ consent to participate in this trial. Many candidates refused to be randomised to receive NAC. This may be one of barriers that prevents carrying out randomised phase III trials of NAC followed by cystectomy versus cystectomy alone. Furthermore, gemcitabine was approved in Japan during the registration period of this trial, which might have led to recommendation not to participate in this trial but to receive gemcitabine/cisplatin instead of MVAC among the investigators.

In this study, OS was better than expected in both arms. We assumed that the 5-year OS would be 45% in the RC arm according to the results from SWOG-8710 [4] and our prior retrospective study [2]. This study included more patients with...
T2 disease than SWOG-8710 (54% versus 40%), which is one of the reasons for the better OS in the RC arm. The 5-year OS in the cystectomy alone group in the MRC trial, including T2 disease in 38%, was similar to that in SWOG-8710 (46% and 43%, respectively) [4, 5]. Furthermore, the lymphadenectomy specified in this trial might have contributed to the longer OS in both arms [13].

The proportions of pT0 in the RC arm and NAC arm were similar to the results of the SWOG-8710 trial [4]. Two large retrospective studies indicated that patients who underwent radical cystectomy for treatment of MIBC and whose pathological tumour stage was pT0 at cystectomy had a benefit for survival [14, 15]. In SWOG-8710, patients with pT0 at cystectomy showed favourable prognoses in both the neoadjuvant and cystectomy alone arms [4]. These findings suggested that a higher incidence of cancer absent upon pathological staging in the NAC arm led to a better outcome in survival than in the RC arm.

Toxicities during NAC were expected and well managed, and no unusual trends were noted. No patient had a delay in surgery due to AEs and no remarkable differences in intraoperative findings and complications were observed between the RC and NAC arms. These results supported the tolerability of two cycles of MVAC. There were no remarkable differences in most of the early and late complications between the arms. Anastomotic leakage was seen more often in the NAC arm than in the RC arm. This may have been affected by preoperative chemotherapy, although previous trials [4, 6] and a large retrospective series [16] did not report the risk. Although the proportion of this complication was not so high, it is suggested

![Figure 2. Survival by treatment group. (A) Overall survival; (B) progression-free survival. *Stratified by clinical stage. RC, radical cystectomy; NAC, neoadjuvant chemotherapy.](https://academic.oup.com/annonc/article-abstract/25/6/1192/2769789/Randomised-phase-III-study-of-neoadjuvant/196)
that surgeons should pay particular attention to intestinal anastomosis for patients who receive NAC. Lymph leakage was seen less often in the NAC arm than in the RC arm, but whether NAC has the potential to prevent lymph leakage is unclear.

We set two cycles of MVAC as the regimen for NAC in this trial. This was mainly because two cycles of MVAC was considered to be tolerable and have therapeutic potential as preoperative chemotherapy according to a previous study [17]. We also took into account the possibility of the ineffectiveness of neoadjuvant MVAC, because a clinical equipoise between treatments with and without NAC for MIBC existed when we started this trial. In the M.D. Anderson Cancer Centre trial that randomised patients with locally advanced bladder cancer to receive either two cycles of neoadjuvant MVAC followed by cystectomy plus three additional MVAC or initial cystectomy followed by five cycles of adjuvant MVAC [18], only 1 of the 70 patients failed to undergo cystectomy after two cycles of neoadjuvant MVAC. Furthermore, there was no significant difference in survival between the arms. These results suggested that delay of cystectomy by two cycles of neoadjuvant MVAC did not affect on overall survival even in non-responders. Our results obtained using two cycles of neoadjuvant MVAC reproduced the clinical benefits that were similarly shown by three cycles of neoadjuvant MVAC in the SWOG-8710 trial. To confirm this, however, a further randomised trial comparing two cycles with three cycles of neoadjuvant MVAC is needed.

In conclusion, this study demonstrated not only favourable OS of patients who received neoadjuvant MVAC but also the tolerability and lack of surgical delay of this treatment. Although NAC with gemcitabine/cisplatin is widely used for MIBC without level I evidence, neoadjuvant MVAC can still be considered promising as a standard treatment.

acknowledgements

We thank the patients and their family members. We are also grateful to the members of the JCOG Data Centre and JCOG Operations Office for their support in preparing the manuscript (Kenichi Nakamura), statistical analysis (Junki Mizusawa, Masashi Shimura), data management (Kazumi Kubota), and oversight of the study management (Haruhiko Fukuda).

funding


disclosure

The authors have declared no conflicts of interest.

references

Appendix

The following institutions (28 from north to south) participated:

- Hokkaido University Hospital
- Sapporo Medical University
- Tohoku University Hospital
- Akita University School of Medicine
- Yamagata University Hospital
- Faculty of Medicine, University of Tsukuba
- Tochigi Cancer Centre
- Chiba University, Graduate School of Medicine
- National Cancer Centre Hospital
- Teikyo University School of Medicine
- Kitasato University School of Medicine
- Niigata Cancer Centre Hospital
- University of Yamanashi Faculty of Medicine
- Hamamatsu University School of Medicine
- Shizuoka Cancer Centre
- Nagoya University School of Medicine
- Mie University School of Medicine
- Kyoto University Hospital
- Osaka Prefectural Hospital Organization Osaka Medical Centre for Cancer and Cardiovascular Diseases
- Nara Medical University
- Faculty of Medicine, Kagawa University
- National Hospital Organization Shikoku Cancer Centre
- National Kyushu Cancer Centre
- Kurume University School of Medicine
- Kyushu University Hospital
- Hara Sanshin Hospital
- Kumamoto University Medical School
- Kagoshima University, Faculty of Medicine

Screening for coronary artery disease after mediastinal irradiation in Hodgkin lymphoma survivors: phase II study of indication and acceptance†

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Received 29 August 2013; revised 15 January 2014; accepted 24 March 2014

Background: Cardiovascular diseases are the most common nonmalignant cause of death in Hodgkin lymphoma (HL) survivors, especially after mediastinal irradiation. We investigated the role of computed tomographic coronary angiography (CTA) as a screening tool for coronary artery disease (CAD) in asymptomatic HL survivors, and related CTA findings to exercise testing and subsequent interventions.

Patients and methods: Patients were eligible for this phase II study if at least 10 years disease-free and treated with mediastinal radiotherapy. Screening consisted of electrocardiogram, exercise testing and CTA. Primary end point was significant CAD (stenosis >50%) on CTA. CTA screening was considered to be indicated for testing in a larger population if ≥6 of 50 CTA scanned patients (12%) would need revascularization. Screening was evaluated with a questionnaire before and after screening.

Results: Fifty-two patients were included, and 48 patients underwent CTA. Median age was 47 years, time since HL diagnosis 21 years. There were 45 evaluable scans. Significant CAD on CTA was found in 20% (N = 9), significantly increased compared with the 7% expected abnormalities (P = 0.01, 95% confidence interval 8.3% to 31.7%). In 11%

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†Presented as poster at the 49th annual ASCO meeting, 31 May–4 June 2013, Chicago, IL, USA.

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