January 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8008-review.doc).

Title: Coronary Artery Calcium Score on low-dose HRCT for lung cancer screening

Author: Teresa Arcadi[1], MD; Erica Maffei[2], MD; Nicola Sverzellati[3], MD; Cesare Mantini[4], MD; Andrea Guaricci[5], MD; Carlo Tedeschi[6], MD; Chiara Martini[3], MD; Ludovico La Grutta[7], MD; Filippo Cademartiri[1,8], MD, PhD

Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 8008

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1
Arcadi et al report an interesting study comparing coronary artery calcium scores computed with traditional methods or using non-gated CT. Despite the work strengths, we recommend addressing the following comments:

1. Provide additional patient details in Table 1, e.g. risk factors, Framingham Heart Score, and so forth.
- This could be interesting and we have those data but there are few considerations. This is a feasibility study that aims at proving the fact that ngCCT can be done and results are somehow in line with conventional gCCT. In addition, since we have no outcome data and the population is small there would be no point in providing this information at this stage. In fact what we are planning is a larger study (>1000 pts with about 2 years follow-up; actually the study is almost done) to verify if the incremental value of CACS as measured on ngCCT is preserved against the stratification with conventional risk factors and scores. As a final remark we have to consider that potential use of CACS in lung cancer screening would we performed in non-primarily cardiovascular individuals. In summary this is a pilot technical paper with the aim of proving the concept. Some more clinical insights will come with larger population. We could not perform clinical studies if we do not perform first a pilot study that shows reliably that we can actually do we want.

2. Explore with multivariable analysis if patients with major delta between different CACS computations can be recognized beforehand with one or more baseline features (e.g. heart rate, body mass index, and so forth).
- This is a nice observation. However, we didn't go into that for several reasons. The main one is that the population is small (this is a cros-oevr feasibility study) and we do not have sufficient heterogeneity and spectrum (i.e. power) of CACS to investigate subgroups.

3. Figure 1: add SD to mean values and interquartile ranges for median values.
- Corrected

4. Figure 3 (and Results): comment on the 2 key outliers in greater detail.
- Corrected both in figure and in text of results

5. Spell out all acronyms at first usage (e.g. CACS in the abstract).
- Corrected

Reviewer 2
This is a well written manuscript that compares quantification of coronary artery calcium scoring by non-gated techniques with traditional thick slice reconstructions as used in lung screening exams with calcium scoring by traditional gated techniques with thin slice reconstructions. The authors demonstrate that there are significant discrepancies in the measurements by these techniques and that bias appears to occur in both directions, although predominantly towards lower calcium scores with the non-gated technique. However, they conclude that calcium scores should still be performed on these lung screening studies since they can add prognostic information to the patient's care.

Abstract: Good
Introduction: Good
Methods: Details on CT scanning such as use of dose modulation on the gated acquisitions should be included.
-       We thank the reviewer for the observation. In fact, the 2 protocols are the standard ones. The ngCCT is a standard low dose spiral CT protocol @ 120kV and 30mAs, while the gCCT is the standard protocol for Calcium score with 150mAs. There was no additional dose modulation in order also to keep the protocol constant without including another variable (software for dose modulation)

Additionally, information on how the CT studies were analyzed, particularly with regard to measurement of intra and inter-observer variability given that at present the manuscript states that only one operator analyzed all of the studies. Was the reader blinded to the type of study (gated or non-gated) and participant?
-       We thank the reviewer for the observation. Yes it was, even though for an experienced operator it is not difficult to recognize a gated CT scan vs. a non gated.

Were repeat readings performed with a time interval between reads? If so, how long? How many studies were reread?
-       We thank the reviewer for the observation. Actually this paragraph got lost during the subsequent revisions. We re-inserted the data under image evaluation.

Results: Good

Discussion: Clinical implications needs to be better defined. The data suggest that there is significant discrepancy between measurement of coronary calcium score as measured by traditional gated CT with thin slice reconstructions and non-gated CT with thicker reconstructions as used for lung screening exams, with bias towards underestimation with non-gated studies, but evidence that reclassification occurs in both directions. Although not evaluated in the current study, the authors suggest that prior studies demonstrate the proven prognostic value of such measurement, but it is not clear that the measurement as made in the manner of the current study (thick slice reconstructions and non-gated) would definitively show similar prognostic value given the variability demonstrated in the current study. Thus, the authors need to justify their conclusion and clinical implications, particularly with focus on how to deal with the discrepancies between the two datasets as demonstrated in their study.
-       The referenced study was performed by us: Sverzellati N et al (2012) Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial. Radiology. Feb;262(2):460-7.
-       The technique applied here is the same applied for the current cross-over feasibility study.
-       Clinically this approach requires additional longitudinal studies with events collection and large

populations.

Thank you again for publishing our manuscript in the *World Journal of Radiology.*

Sincerely yours,

Prof. Dr. Filippo Cademartiri, MD, PhD, FESC, FSCCT
Cardio-Vascular Imaging Unit - Giovanni XXIII Clinic
Via Giovanni XXIII, 7 – 31050 – Monastier di Treviso (TV) - Italy
Tel. +39 0422 896710 - Fax +39 0422 896507
E-mail: filippocademartiri@gmail.com