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Review

Cardiac toxicity of lung cancer radiotherapy☆

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ABSTRACT

Radical radiotherapy of lung cancer with dose escalation has been associated with increased tumor control. However, these attempts to continually improve local control through dose escalation, have met mixed results culminating in the findings of the RTOG trial 0617, where the heart dose was associated with a worse overall survival, indicating a significant contribution to radiation-induced cardiac morbidity. It is, therefore, very likely that poorly understood cardiac toxicity may have offset any potential improvement in overall survival derived from dose escalation and may be an obstacle that limits disease control and survival of patients. The manifestations of cardiac toxicity are relatively common after high dose radiotherapy of advanced lung cancers and are independently associated with both heart dose and baseline cardiac risk. Toxicity following the treatment may occur earlier than previously thought and, therefore, heart doses should be minimized. In patients with lung cancer, who not only receive substantial heart dose, but are also older with more comorbidities, all cardiac events have the potential to be clinically significant and life-threatening.

Sophisticated radiation treatment planning techniques, charged particle therapy, and modern imaging methods in radiotherapy planning, may lead to reduction of the heart dose, which could potentially improve the clinical outcomes in patients with lung cancer. Efforts should be made to minimize heart radiation exposure whenever possible even at doses lower than those generally recommended. Heart doses should be limited as much as possible.

A heart dosimetry as a whole is important for patient outcomes, rather than emphasizing just one parameter.

1. Introduction

Lung cancer is currently the most commonly diagnosed cancer in the world. The estimated number of diagnosed lung carcinomas worldwide in 2018 is 2.1 million. It is also the most common cause of cancer death, the estimated number of deaths in 2018 is 1.7 million.[1] Lung carcinomas are generally divided into two basic types: non-small cell lung cancer (NSCLC) that accounts for 80–85% of total number of lung carcinomas, and small cell lung cancer (SCLC) accounting for the remaining 15–20%. Both types differ from each other by biological behaviour and prognosis, as well as by the treatment strategy.

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Radiotherapy (RT) can be indicated in a lung cancer treatment algorithm, under certain circumstances, at any stage of the disease with different therapeutic goals. Approximately 30% of NSCLC are considered to be locally advanced, comprising both stage IIIA and IIIB according to the current American Joint Committee on Cancer (AJCC) staging system.[2] For patients with unresectable stage III cancer, chemoradiotherapy is the treatment of choice, either concomitant (for patients with a good general condition and a weight loss of less than 5% in the previous 3 months), or sequential (for patients with moderate general condition, weight loss greater than 5% and a large volume to be irradiated).[3] However, locoregional relapse remains common and is also associated with inferior overall survival (OS).[4] Most patients with SCLC present with hematogenous metastases, also approximately one third present with limited disease confined to the chest.[5] In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus radiotherapy.[6,7] Although SCLC is highly sensitive to initial treatment, most patients eventually die of recurrent disease.[5]

2. Limitations of dose escalation in radical radiotherapy of lung cancer

Radical RT of NSCLC with dose escalation has been associated with increased tumor control, leading to a number of promising phase II trials.[8–10] However, these attempts to continually improve local control through dose escalation have delivered mixed results culminating in the findings of the RTOG (Radiation Therapy Oncology Group) trial 06172, multi-institutional randomized controlled phase III trial. In this 2×2 factorial design trial, patients with stage III NSCLC all received weekly carboplatin and paclitaxel chemotherapy with concurrent radiation in 2 Gy daily fractions followed by two cycles of consolidative chemotherapy after the completion of radiation. Patients were randomized to receive either 60 or 74 Gy with or without cetuximab. At the first interim analysis, the monitoring committee established that the trial had crossed the futility boundary with respect to the 74 Gy arm, and this high dose arm was closed. The results of this trial showed a significantly higher number of deaths in the 74 Gy arm. The median OS was 28.7 months in 60 Gy arm compared to 19.5 months in 74 Gy arm ($p = 0.0007$; HR 1.56, 95% CI: 1.19–2.06). In multivariate analyses, the heart dose was also reported among the predictors of worse survival. In other words, the heart dose was associated with a worse OS at a median follow-up of 2 years, indicating a significant contribution to radiation-induced cardiac morbidity and still relatively soon after treatment.

Poorly understood toxicity to an organ at risk (OAR) is, therefore, very likely to offset any potential improvement in OS derived from dose escalation[11] and pulmonary and cardiovascular toxicity may be obstacles that limit disease control and survival of patients.[12]

The current relationship of various professional authorities to excessive dose escalation is evident from the following information. ASTRO (American Society for Radiation Oncology)[13] uses a dose of 60 Gy as a standard in its guidelines. NCCN (National Comprehensive Cancer Network) guidelines[14] now recommend the use of doses of 60–70 Gy in radical radiotherapy. ESMO (The European Society for Medical Oncology) guidelines[15] state that “dose in excess of 66 Gy is not recommended outside trials”. In the United Kingdom, a dose of 55 Gy in 20 fractions of 2.75 Gy per fraction is the most commonly used regimen, with or without concomitant systemic treatment.[16]

On the other hand, rather than prescribing the same fixed dose to all patients with locally advanced tumor, isotoxic radiation therapy is a new approach allowing personalized treatment planning based on the individual characteristics of the tumor and the patient. This tailored approach is based on predefined dose limits of organs at risk. The treatment plans are designed to apply the maximum reachable biological equivalent dose (BED) into the tumor until reaching dose limits. This approach is facilitated by the increased use of highly conformal radiotherapy techniques, e.g. intensity modulated radiotherapy (IMRT).[12] However, in order for this approach to be applied, it is necessary to know the precise relationship of dose limits of the OAR and the toxic manifestations resulting from their overcoming, especially in the heart, which is the least explored in this respect.

For limited-stage SCLC, the optimal dose and schedule of RT have not been established. Based on the randomized phase III trial, INT 0096,[17] 45 Gy in three weeks (1.5 Gy twice daily) is widely recommended. If using once-daily RT, higher doses of 60–70 Gy should be used.[18] The current randomized trial CALGB 30610/RTOG 0538[19] is comparing the standard arm of 45 Gy in three weeks to 70 Gy in 7 weeks.

3. Manifestations of cardiac toxicity in radiotherapy of lung cancer

Although RT-induced cardiac toxicity is known from patients irradiated for Hodgkińs lymphoma or breast cancer,[20,21] the clinical relevance of these manifestations in patients with advanced lung cancer is not clear and data regarding RT-induced cardiac toxicity in the population of patients with NSCLC and SCLC are limited.[11] This is because there are few long-term survivors to experience toxicity, because the symptoms typically occur with a long latency time and also due to poor prognosis of these patients. However, RT-induced cardiac events after RT of Hodgkin’s lymphoma and breast cancer may occur at earlier intervals.[22] Due to the fact that patients with Hodgkin’s lymphoma (less those with breast cancer) are usually younger and have a better prognosis, radiotherapeutic practice seeks to avoid cardiac toxicity in these patients. However, this did not apply to patients with advanced lung tumors who have a median survival of generally less than 2 years and where pneumonia and oesophagitis are the main manifestations of toxicity. This is also the reason why many studies do not contain cardiac constraints or are very benevolent, e.g. in the RTOG trial 0617 V40 (the proportion of heart volume receiving at least 40 Gy) was allowed to be under 100% and heart priority was up to the fifth in line, behind the spinal cord, the lungs, the oesophagus and the brachial plexus.2 Moreover, several studies also reported an increased number of cardiac deaths after postoperative RT of stage I-III NSCLC.[23,24]

It is increasingly evident that RT-associated cardiac morbidity and mortality after treatment of locally advanced lung cancers may occur earlier than previously thought and, therefore, heart doses should be minimized along with future efforts to dose escalation.[12,25]

3.1. *Clinical manifestations of cardiac toxicity*

RT-associated cardiac toxicity can be clinically manifested either as acute injury – pericarditis (uncommon, usually transient, but can be chronic), or as late injury in the form of congestive heart failure (CHF), ischemia, coronary artery disease (CAD), myocardial infarction (MI), chronic pericardial effusion. These late manifestations begin to occur several months to years after RT.[26] However, each study defines different clinical manifestations as heart events. Therefore, these events must be explicitly named. It is not clear how radiation can increase the risk of early cardiac toxicity, but considering the diversity of types of events, the mechanism is likely to be multifactorial, and there are distinct etiologies for different types of RT-associated cardiac toxicities.[27] The heart is complex and may malfunction in ways other than ischemia-induced contractile insufficiency, as previously reported in early analyses of RT-associated cardiac toxicity. This heterogeneity is illustrated by the CTCAE (Common Terminology Criteria of Adverse Events) grading, listing 34 distinct cardiac events.[28] Also RTOG mentions angina, arrhythmia, pericarditis, pericardial effusion, and heart failure across different grades of severity.[29]

In 2017, Wang et al.[30] published a study evaluating the effect of the heart dose in 112 patients treated in 6 different prospective dose escalation studies. A total of 26 patients (23%) had one or more heart events at a median of 26 months to the first event – pericardial effusion (7), myocardial infarction (5), unstable angina pectoris (3), pericarditis (2), arrhythmia (12) and heart failure (1). Competing risk-adjusted event rates for patients with mean heart dose (MHD) < 10 Gy, 10–20 Gy, or > 20 Gy were 4%, 7%, and 21%, respectively at two years and 4%, 13% and 41%, respectively at 4 years. Patients with MHD > 20 Gy had significantly higher rate of cardiac events than patients with MHD < 10 Gy (HR, 5.47; $p < 0.001$) or 10–20 Gy (HR, 2.76; $p = 0.03$). Event rate did not differ significantly between patients with MHD 10–20 Gy vs. MHD < 10 Gy (HR, 1.98; $p = 0.25$). Interestingly, heart doses were not associated with OS, two-year OS for patients with MHD < 10 Gy, 10–20, and >20 Gy was 50%, 40%, and 44%, respectively ($p = 0.73$).

The same authors performed a pooled post-hoc analysis of previously studied patients from the above-mentioned study, and assessed associations between radiation dose to different cardiac subvolumes - whole heart, left ventricle (LV), right atrium (RA), and left atrium (LA), and different toxicity endpoints – pericardial events, ischemic events, and arrhythmic events. Pericardial events were significantly associated with whole heart, LA, and RA dose, but not LV dose. These events had the greatest number and strength of associations with heart subvolume dose. Ischemic events were significantly associated with whole heart and LV dose, but not LA or RA dose. And arrhythmic events showed borderline significant associations with whole heart, LA, and RA dose, but no association with LV dose. LV dose was associated with ischemic events only. Thus, the common perception that acute coronary syndrome is related to LV dose may apply to patients with lung cancer.[27]

In the study published also in 2017, Speirs et al.[11] retrospectively analyzed dosimetric parameters affecting cardiac toxicity and OS in a population of 322 patients with locally advanced NSCLC with a focus on the heart dose. Most patients were treated with 3D-CRT (3-dimensional conformal radiotherapy) (60%) at a median dose of 66 Gy. As manifestations of toxicity, they evaluated pericardial effusion, arrhythmia, acute coronary syndrome, valvular defects, CHF and cardiac death. Median heart V50 was significantly higher (20.8% versus 13.9%, $p < 0.0001$) for patients with cardiac toxicity with CTCAE grade >1. Cardiac toxicity was grade 2 in 27.5%, grade 3 or more in 24% and grade 5 in 0.2% of patients. When startified by heart V50 < 25% versus V50 > 25%, the 1-year OS rates were 40.2% versus 46.8% and the 2-year OS rate were 45.9% versus 26.7% ($p < 0.0001$). Sustaining the value of V50 < 25% is associated with almost 20% absolute improvement of the 2-year OS. Multivariate analysis then showed that the increasing heart V50 (HR = 1.23, $p < 0.0001$) and heart volume (HR = 1.12, $p < 0.0001$) are independent negative predictors of OS.

Dess et al.[31] evaluated patient- and treatment-related factors associated with clinically significant cardiac events and attempted to determine the effect of these events on OS in 125 patients with stage II-III NSCLC from 4 prospective studies. Nineteen patients had cardiac event grade 3 or more at a median of 11 months, with a 24-month cumulative incidence of 11%. Thirteen patients experienced grade 3 toxicity (acute coronary syndrome, CHF), 3 patients had grade 4 (surgical intervention for severe pericardial effusion, emergent balloon valvuloplasty of aortal stenosis) and 2 patients had grade 5 toxicity (cardiac arrest – pre-treatment multivessel CAD and CHF). Grade >3 cardiac events (HR 1.76; 95% CI 1.04–2.99) were associated with a decrease of OS. Median MHD was 11 Gy (range 0.3–46 Gy) when trying to keep the following heart dose constraints: V40 < 100%, V65 < 33%. The heart dose was not significantly associated with OS in either univariate or multivariate analysis.

In contrast, Schytte et al.[33] found no relationship between heart dose and cardiac events or survival in stage I-III patients treated in studies with RT or radiochemotherapy. Most patients in these studies received conventional doses of 60–66 Gy and were not included in prospective studies. In a large retrospective study (468 patients), Tucker et al.[32] found no evidence that heart exposure affected early OS (within the first 2 years of treatment) after accounting for other relevant factors, particularly lung dose.

As can be seen from most studies, the risk of cardiac toxicity is likely to increase continuously with heart dose but the possibility of minimizing the dose is limited by competing priorities such as tumor control and doses to other OAR, especially the lungs. Coverage of target volume should only be seldom compromised by adhering to the heart dose constraints. However, it is still worth trying to limit the heart dose as much as reasonably achievable. Guidelines are needed to help clinicians balance the competing priorities of minimizing dose to the heart and other OAR.[27] Further studies are warranted to better understand the impact of hypofractionated schedules on the cardiac toxicity.[26]

3.2. *Impact of pre-existing cardiac comorbidities on manifestations of cardiac toxicity of radiotherapy*

Despite the fact that the prognosis of patients with lung tumors is inherently bad, they usually have high heart doses and may also have more comorbidities and smoking history, which increases the risk of developing cardiac events and shortens the latency between RT and onset of cardiac events.[27] Patients with lung tumors are more likely to have other risk factors for cardiac toxicity, such as pre-existing heart disease, which reduces their tolerance and predisposes them to earlier events. The risk of developing cardiac events depends not only on dose and irradiated volume, but also on baseline patient cardiac risk factors (age, diabetes mellitus, smoking, hypertension, LDL and HDL cholesterol levels, family history of early myocardial infarction aged less than 60 years) and cardiotoxic chemotherapy.[26] Although there is currently no evidence that successful treatment of traditional cardiac risk factors has changed the nature of RT-associated cardiac disease, it is advisable to try to optimize risk profiles.[26]

In the above-mentioned study of Dess et al.,[31] pre-existing cardiac disease was reported to be significantly associated (HR 2.96; 95%CI 1.07–8.21; p = 0.04) with the occurrence of cardiac event grade 3 or more. In patients with pre-existing cardiac disease, the 24-month cumulative incidence of event grade 3 or more was 21% (95% CI 7–35%). These events were associated with a decrease in OS (HR 1.76; 95% CI 1.04–2.99), regardless of the presence or absence of pre-existing cardiac disease. Pre-existing cardiac disease was defined in this study as the presence of either pre-existing ischemic heart disease (acute myocardial infarction, coronary artery bypass grafting procedure, angioplasty or stent placement, or diagnosis of coronary artery disease) or CHF. Interestingly, Janssen-Heijnen et al.[34] reviewed nearly 4000 patients with lung cancer in the Netherlands and noted that a diagnosis of concomitant cardiovascular disease was 23%, nearly twice that of the general population.

Individualized, more stringent heart dose constraints may be needed in those patients with a pre-existing cardiac disease. In the light of these findings, it is clear that future thoracic RT studies should stratify patients based on pre-existing cardiac status to enable a more meaningful analysis of cardiac events.

4. Pitfalls of the contouring of the heart as an organ at risk

In 2010, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) Report highlighted the need for guidelines to reduce inter-observer variation in cardiac contouring.[26] Despite this, the contouring of whole heart and its clinically significant subregions is challenging because their structural definitions based on current imaging methods used in RT planning (i.e. computed tomography) are inaccurate. The boundary of the heart is difficult to distinguish from the liver and the diaphragm, but it is even more demanding to determine the upper border in the area of large vessels.[26] There is also uncertainty as to which region of the heart is the most important in terms of RT-induced toxicities.[26] It is necessary to differentiate the definition of the whole organ or its various subregions with different functional consequences (whole heart vs. pericardium vs. coronary arteries vs. various cardiac subvolumes). For example, clinical data on the risk of pericardial effusions are better correlated with parameters derived from the dose-volume histogram (DVH) of the pericardium rather than from DVH of the whole heart.[35]

5. Heart dose constraints

There are currently no consistent quantitative recommendations regarding dose constraints on the heart (and its subvolumes) in RT of lung tumors. This is due to the fact that, as mentioned above, many studies regarding RT of lung tumors did not have these heart dose constraints at all. Exceptions were studies by Wang et al.,[30] Dess et al.[31] and Speirs et al.,[11] who used the following heart dose constraints: V40 < 100%, V40 < 100% and V65 < 33%, and V50 < 25%, respectively. The latter study concludes that maintaining V50 below 25% is associated with almost 20% absolute improvement of the 2-year OS. This is in line with the latest NCCN recommendations (version 3.2019) - V50 < 25%, MHD < 20 Gy.

Widely used recommendations from the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) information do not take into account the different role of the heart as OAR in the RT of various thoracic tumors. However, it is suggested, when trying to reduce the risk long-term cardiac mortality to be less than 1%, to keep the whole heart V25 < 10%. Pericardial dose constraints are suggested to be as follows: mean dose <26 Gy and V30 < 46% - the risk of pericarditis should be less than 15%.[36]

Perhaps the most relevant recommendation of heart dose constraints comes from the ongoing trial RTOG 1308 (Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II to IIIB NSCLC), in which heart dose constraints of V30 < 50% and V45 < 35% are set. Their usability in this study was verified in the below-commented dosimetric feasibility study.

To our best knowledge, there are no relevant dose-volume recommendations for cardiac subvolumes but above mentioned QUANTEC recommendation for pericardium. However, as also already mentioned, some studies, as that by Wang et al.,[30] hypothesized that arrhythmia would show the greatest association with atrial dose, but only weak association was eventually observed. Arrhythmia is relatively common and often due to concurrent acute ilness, and thus may be non-specific endpoint. Ischemic events are associated with LV dose and left anterior descending artery (LADA) dose, which was confirmed by Wang et al.[30] and van den Bogaard et al.[37]

In general, the following basic recommendations should be followed. Efforts should be made to minimize heart radiation exposure whenever possible even at doses lower than those generally recommended. Heart doses should be limited as much as possible.[38] A heart dosimetry as a whole is important for patient outcomes rather than emphasizing just one parameter.[11] It is also unclear which regions of the heart are most susceptible for radiation injury.

6. How to further reduce the radiation exposure of the heart

Sophisticated radiation treatment planning techniques, charged particle therapy with protons and carbon ions, the use of modern imaging methods in RT planning and the use of image-guided radiotherapy (IGRT) may provide increased flexibility to generate more conformal treatment plans and reduce heart dose, which could potentially improve the clinical outcomes in patients with lung cancer.[39]

Patients with lung cancer treated with IMRT have lower heart dose than those treated with conventional 3D-CRT, as demonstrated by the secondary analysis of RTOG trial 06172 (V40 6.8% vs. 11.4%; $p < 0.01$). The value of V40 was also inversely associated with OS. In an earlier retrospective study, Speirs et al.[11] report on lower cardiac toxicity in patients treated with IMRT ($p < 0.0001$). Another dose-volume parameter was used for numerical comparison - median heart V50 were significantly higher (24.7% vs. 10.2%, $p < 0.0001$) for 3D-CRT versus IMRT, respectively.

There is controversy over the use of proton RT. This type of RT generally allows dose reduction in OAR compared to photon RT due to the physical properties of the proton beam, with essentially no dose delivered distal to the characteristic Bragg peak.[40,41] The ongoing trial RTOG 1308 compares IMRT technique vs. passive scattering proton therapy (PSPT). In 2016, Giaddui et al.[42] published a study to evaluate the feasibility of the dosimetric compliance in the above-mentioned RTOG 1308 trial. In this study, IMRT and PSPT plans were compared in 26 patients. Dosimetric compliance criteria for heart were V30 < 50% and V45 < 35%. This study was conducted when designing the new and more stringent dose constraints now in place for the RTOG 1308 clinical trial to test if these criteria are achievable. PSPT plans led to a lower dose exposure of normal structures, specifically in the heart: V5 (19 vs. 47%), V30 (11 vs. 19%), V45 (7.8 vs. 12.1%), V50 (7.1 vs. 9.8%), MHD (7.7 vs. 14.9 Gy). The deviation unacceptable rates in the heart V30 and V45 were 8 and 4, respectively, in IMRT plans; meanwhile, all PSPT plans met the heart V30 and V45 compliance criteria. Heart V5, MHD, V30, V45 and V50 were 59% ($p < 0.001$), 48% ($p < 0.001$), 41% ($p < 0.001$), 35% ($p = 0.029$) and 27% less in PSPT plans when compared with IMRT plans. On the contrary, Berman et al.[43] have come to different results – they reported 4.6% higher MHD in PSPT plans as compared with IMRT plans.

The use of PET/CT examination in RT planning of lung cancer has crucial impact on the precise determination of target volumes, precise staging of the disease and thus also impact on possible change of treatment strategy. Change in target volume sizes leads to a change in the irradiated volume of OAR. In our previously published study, we observed that the change of target volumes size has significant impact on the radiation exposure of the heart. Incorporating the PET/CT to the planning led to a decrease in all analyzed dosimetric parameters: the median V33 decreased from 18% + 22.5 (range 0–47%) to 16% + 24 (range 0–51%), $p = 0.007$; and the median MHD from 17.2 Gy + 17.5 (range 1.6–31.8 Gy) to 14.4 Gy + 17.8 (range 0–31.8 Gy), $p = 0.0017$.[44] Deniaud-Alexandre et al.[45] also reported the impact of changes in target volumes on the irradiation of OAR. They evaluated, inter alia, radiation exposure of the heart (V36) in 92 patients. The volume of GTV decreased by PET/CT in 21 (23%) patients. The percentage of total heart volume receiving more than 36 Gy (V36) decreased in 14 patients (median 65.5%).

How to ensure the delivery of an accurate dose to the target volume while minimizing the irradiation of OAR remains a big challenge for radiation oncologists, especially due to the positioning error between fractions. IGRT technology can help to ensure accurate dosing of the target volume and reduce radiation damage to the surrounding OAR.[46] IGRT can be achieved using the following technologies: (1) online correction (during the course of fractional treatments, two-dimensional or three-dimensional images of the patients are acquired and compared to the planned image after positioning to determine the positioning error, which is corrected immediately);[47] (2) cone beam CT (CBCT) adaptive RT (new extension of IGRT technology that allows for feedback of the target tumor volume and position changes during treatment to analyze the difference between the original plan and the treatment and to obtain real-time anatomical images in order to re-design the treatment plan);[48] (3) breath-holding (temporal elimination of lung cancer movements); (4) respiratory gating control (technique that collects images from different respiratory phases in lung cancer patients and reconstructs images by using four-dimensional CT (4D-CT));[49] and (5) real-time X-ray tracking technology.[47]

7. Conclusions

The manifestations of cardiac toxicity are relatively common after high dose thoracic RT and are independently associated with both heart dose and baseline cardiac risk. Toxicity following the treatment of advanced lung cancers may occur earlier than previously thought and, therefore, heart doses should be minimized. In patients with lung cancer who not only receive substantial heart dose but are also older with more comorbidities all cardiac events have the potential to be clinically significant and/or life-threatening.[27] Sophisticated radiation treatment planning techniques (e.g. IMRT), charged particle therapy with protons, modern imaging methods in RT planning and IGRT may lead to reduction of the heart dose, which could potentially improve the clinical outcomes in patients with lung cancer.

According to the available evidence-based data, it seems that the most relevant heart dose constraints are V30 < 50% and V45 < 35%.

Future studies can identify patients with elevated cardiac risk by using pretreatment cardiac risk algorithms for screening[11] and more studies are needed to find out whether some cardiac subvolumes should take priority over others during the treatment planning process.

Conflict of interest

None declared.

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