Risk factor of pneumonitis on dose-volume relationship for chemoradiotherapy with durvalumab: Multi-institutional research in Japan

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Abstract

Objectives: To estimate appropriate dose-volume parameters for avoidance of pneumonitis in use of chemoradiotherapy and durvalumab for treatment of lung cancer.

Materials and methods: Patients with non-small cell lung cancer treated with concurrent chemoradiotherapy followed by durvalumab at 9 centers were enrolled in the study. Three-dimensional radiotherapy, intensity modulated radiotherapy, and proton beam therapy were used. The frequency and severity of pneumonitis and the dose-volume relationship for normal lung were evaluated. Univariable and multivariable analyses were conducted to identify risk factors. A covariate adjusted hazard ratio was then estimated for the percentages of normal lung volume irradiated at ≥X Gy (Vx) (X = 5–40) and lung volume non-irradiated at ≥X Gy (X = 5–40), with the covariates selected in the variable selection. Cumulative incidence functions and covariate adjusted hazard ratios were also estimated for dichotomized variables, with estimated cut-off points.

Results: A total of 91 patients were enrolled in the study. The median time from the start of radiotherapy to development of pneumonitis was 4.1 months. Pneumonitis was observed in 80 patients (88%), including grade 2 or severe pneumonitis in 31 (34%) and ≥ grade 3 pneumonitis in 11 (12%). Pneumonitis was inside the irradiation field in 73 of the 80 patients (91%). The selected factors for ≥ grade 2 pneumonitis were V20, and primary site (upper lobe) in multivariable analysis. The cut off value of V20 was 18.99%, and there was a significant difference between V20 of < 18.77 and ≥ 18.77.

Conclusion: Though there are some limitation of this study, the basic concept of concurrent chemoradiotherapy with emphasis on V20 remains unchanged in use of durvalumab. However, we recommend reduction of V20 to as small a value as possible in use of this therapy.

Introduction

With recent progress of immune therapy, the indication for immune checkpoint inhibitors (ICIs) has expanded in cancer treatment. In 2017, the efficacy of durvalumab after concurrent chemoradiotherapy (CCRT) was suggested in the phase III PACIFIC
study [1–2], and this approach is now widely used as a standard therapy for unresectable locally advanced non-small cell lung cancer (NSCLC). However, an ICI has a risk of an autoimmune response, including interstitial pneumonitis, and this raises a concern about an increased risk of radiation pneumonitis with use of durvalumab.

The risk of radiation pneumonitis is correlated with various factors, such as combined chemotherapy, radiotherapy, age, poor performance status, smoking history, poor lung function, co-existence lung disease of chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cytokines or biomarker level, and dosimetric factors of radiotherapy [3–9]. In radiotherapy, the dose-volume relationship for the normal lung is one of the most important factors, and this has been evaluated using a dose-volume histogram (DVH) in previous studies of CCRT. The importance of the lung volume irradiated at ≥20 Gy (V20) has been established for radiation pneumonitis [7,10], and parameters such as V10, V30, and mean lung dose (MLD) have also been suggested as significant risk factors for radiation pneumonitis [7,10–19]. In the PACIFIC study, the incidence of pneumonitis was infrequent [2]; however, it is unclear if previous dose-volume parameters can be used for radiotherapy with durvalumab. In this study, we evaluated DVHs of patients with locally advanced NSCLC who received CCRT followed by durvalumab at 9 centers, and we analyzed risk factors for pneumonitis.

Material and methods

Patients

Patients who received durvalumab following CCRT at 9 centers in Ibaraki prefecture from March 2018 to August 2020 were enrolled in this study. Each institutional review board approved this study. Written informed consent was obtained from all patients before treatment was administrated.

Radiation therapy

Three-dimensional radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT) including tomotherapy, and proton beam therapy (PBT) were available at the 9 centers, and patients were treated with all these modalities. In PBT, an equivalent dose to photon therapy was used based on a relative biological effectiveness of 1.1 [20]. The target policy differed among the centers and elective nodal irradiation (ENI) was performed at some centers. Respiratory synchronization, breath holding, and abdominal compression were used for respiratory control. Normal lung volume was contoured as the bilateral lung volume minus the clinical target volume (CTV). Lasso-based variable selection with Bayesian information criteria was also performed.

Analysis

The DVH was calculated on a treatment planning system at each center. Pneumonitis was graded according to CTCAE version 4.0. The end point was defined as the time to occurrence of pneumonitis (≥grade 2 or ≥ grade 3) while treating death as a competing risk. A univariable subdistribution hazard model was used for explanatory variables [21–22] of age (≥68 vs. < 68), gender, performance status (PS, 0 or 1 vs. 2 or 3), stage (stage II vs. III vs. others), pathology (adenocarcinoma vs. squamous cell carcinoma vs. others), programmed cell death ligand-1 (PD-L1) status, serum value of sialylated carbohydrate antigen (KL-6), smoking history, Brinkman index, presence of COPD, ILD, pulmonary infection, chemotherapy regimen (cisplatin (CDP) + vinorelbine (VNR) vs. carboplatin (CBDC) + paclitaxel (PTX) vs. CDDP + pemetrexed (PEM) vs. CDDP + tegafur, gimeracil, oteracil potassium (TS-1) vs. others), radiotherapy modality (3D-CRT vs. 3DCRT + IMRT vs. IMRT vs. PBT), respiratory control method (synchronization vs. depression vs. abdominal compression vs. none), treatment field (ENI vs. involved field radiation therapy (IFRT), number of treatment fields shrinkage times, total dose, CTV, planning target volume (PTV), MLD, and percentages of normal lung volume irradiated at ≥X Gy (Vx) (X = 5–40) and lung volume not irradiated at ≥X Gy (remnant lung volume, RLVx) (X = 5–40).

Lasso-based variable selection based on Bayesian information criteria was conducted using the above candidate explanatory variables to identify risk factors [23–24]. The covariate adjusted hazard ratios (HR) for Vx and RLVx were then estimated using a subdistribution hazard model with the covariates selected in the variable selection. In these analyses, Vx and RLVx (X = 5–40) were treated as categorical variables divided into four with estimated quartiles. The following parameters previously reported as significant factors for radiation pneumonitis were also evaluated: Vx (>40% [15], >60% [13]) V10 (>30% [15], >35% [15]) V20 (>25% [7], 35% [6,11]), V30 (>20% [15]), and MLD (15 Gy, 18 Gy [11,19]). A cumulative incidence function was also estimated for each level of the above categorized variables. Time-dependent ROC curve analysis [25–26] was then applied for Vx and RLVx (X = 5–40), and the time-dependent AUC and cut-off points that maximized sensitivities and specificities at 6 months from irradiation were estimated. Cumulative incidence functions and covariate adjusted HRs were all estimated for the dichotomized variables with determination of cut-off points. P < 0.05 was defined as significant in all statistical tests. R ver. 4.0.3 (R Core Team) and SAS (SAS Institute Inc.) were used for the analyses.

Results

Patients

The characteristics of the 91 patients enrolled in the study are shown in Table 1. The cohort included 67 males and 24 females, and the median age was 68 years old (range, 37 to 86 years). Performance status was 0, 1, 2, and 3 for 63, 22, 4, and 2 cases; the tumor stage was II, IIIA, IIIB, IIE and IV in 2, 35, 35, 12, and 1 cases, and there was postoperative recurrence in 6 cases. One stage IV case had a small brain metastasis and was treated with stereotactic radiotherapy, after which CCRT followed by durvalumab was indicated. The pathology was adenocarcinoma, squamous cell carcinoma, and others in 34, 37 and 20 cases, respectively.

Of the 74 cases in which PD-L1 was evaluated, the level was < 1%, 1–10%, 12.5–50%, 62.5–75%, 80–90%, and 95–100% in 15, 16, 25, 9, and 3 cases, respectively. KL-6 was also measured in 74 cases, and the median value was 305 U/ml (range, 138–2103 U/ml). COPD was present in 27 patients, 5 had ILD, and one patient had mycobacterium intracellulare before the start of CCRT. A total of 82 patients had a smoking history and 26 were current smokers. The median Brinkmann index was 900 (range, 0 to 3300).

A summary of treatment is shown in Table 2. Radiotherapy with 3DRT, IMRT, a combination of 3DRT and IMRT, and PBT was conducted in 67, 12, 10 and 2 patients, respectively. The treatment field was ENI in 33 cases and IFRT in 58. The median treatment dose was 60 Gy (range, 45 to 66 Gy). Adaptive radiotherapy was performed and the number of shrunk targets were 0, 1, 2, 3, and 4 in 3, 68, 17, 2, and 2 cases, respectively.

The mean follow-up period was 14.8 months (range, 3.1 to 31.5 months) and 81 patients (89%) were alive at the last follow up. Durvalumab were administered 1–26 times (median, 11 times). At the last follow-up, durvalumab was ongoing in 27 cases, and 23 had completed administration for 1 year. However, durvalumab...
was interrupted in 41 patients due to disease progression or toxicities.

**Pneumonitis**

The median time from the start of therapy to development of pneumonitis was 4.1 months (range, 1.9 to 16.4 months). Pneumonitis developed in 80 cases (88%), including grade 2 or severe pneumonitis in 31 (34%) and grade 3 pneumonitis in 11 (12%).

Pneumonitis was inside the irradiation field in 73 of the 80 cases (91%). In the 7 cases with pneumonitis spreading outside the irradiation field, grade 3 or severer pneumonitis occurred in 5 (grade 1: 2: 3: 4: 5 = 1: 1: 2: 2: 1) (Table 3).

In univariable analysis, tumor location (upper lobe), ILD, PBT, total dose, Vx (x = 10–40), and remnant lung dose of < 10 Gy and 15 Gy were significantly associated with the incidence of grade 2 pneumonitis; and PS, location, chemotherapy (CDDP + VNR vs. CBDCA + PTX or others), radiation modality (3DCRT vs. others), respiratory control, PTV, and Vx (x = 10–40) were significant factors associated with the incidence of grade 3 pneumonitis (Table 4).

Based on lasso variable selection, V 20 and primary site (upper lobe) were selected as the prognostic factors for grade 2 pneumonitis, however no variable was selected for grade 3 pneumonitis. So the primary site was treated as a covariate factors for estimating covariate adjusted HR for grade 2 pneumonitis. The sensitivity and specificity were calculated for V 20 = 20%, 25%, 30%, and 35%. The sensitivity was reduced and specificity was enhanced as the cut-off value increased (Fig. 2). The cut-off values for Vx (x = 5–40) are shown in Fig. 3. The AUCs were all > 0.7, indicating that they were relatively reliable.

Among previously suggested parameters, V 10 > 30% (p = 0.037 for grade 2), > 35% (p = 0.017 for grade 3), V 20 > 25% (p = 0.026 for grade 3), 30% (p = 0.011 and 0.009 for grade 2 and 3), and 35% (p < 0.001 for grade 2), and MLD > 15 Gy (p = 0.017 for grade 2) and 18 Gy (p = 0.003 for grade 3) were also significant factors according to cumulative incidence analysis.

**Discussion**

In chemoradiotherapy for lung cancer, radiation pneumonitis is one of the most important toxicity. Many parameters have been proposed as significant factors for radiation pneumonitis, with the best known being V 20. In 1999, Graham et al. found that V 20 was significantly correlated with the incidence and grade of radiation pneumonitis, and suggested that a treatment plan with V 20 > 35% should not be used because fatal pneumonitis occurred...
in a patient at this V20 value. In this report [10], 42% of the patients received some form of chemotherapy, and most received concurrent or pre-irradiation chemotherapy with a cisplatin regimen. Then, in 2005, Tsujino et al. reported the significance of V20 in CCRT [7]. The incidence and grade of radiation pneumonitis were shown to differ significantly between V20 > 25% [7].

The efficacy of ICIs has subsequently been established in cancer treatment, and durvalumab is now used after CCRT. However, ICIs have off-target effects and toxicities, including interstitial pneumonitis. Thus, there may be an increased risk of pneumonitis due to potential overlapping radiation and chemical pneumonitis in CCRT plus durvalumab for NSCLC. However, criteria for DVH parameters have not been established for this procedure.

Biologically, radiation pneumonitis occurs between 3 weeks up to 6 months after radiation exposure [27]. In our study, the median time from the start of therapy to development of pneumonitis was 4.1 months, and compatible to this report. In our study, ≥ grade 2 and ≥ grade 3 pneumonitis occurred in 34% and 12% of cases, respectively, which are relatively high compared to previous studies. The incidence of ≥ grade 3 pneumonitis was 4.5% in the PACIFIC trial [2], and the incidences of ≥ grade 2 and ≥ grade 3 pneumonitis were 24% (17/71) and 4.2% (3/71) in the CCRT reported by Tsujino et al. [7]. The reason for the higher incidences in the current study is unclear.

Pneumonitis caused by factors other than radiotherapy was also present, including drug induced pneumonitis, and we did not separate this from radiation pneumonitis because it is difficult to distinguish these conditions. However, a certain number of severe pneumonitis that were not dependent on radiotherapy were thought to occur, considering that 5 of the 7 cases of pneumonitis outside the irradiation field were thought to occur, considering that 5 of the 7 cases of pneumonitis outside the irradiation field were thought to occur. How-
in-field pneumonitis were 28% and 6.5%, respectively, which are similar to those found by Tsujino et al. The high general incidence of pneumonitis may have been due to the lack of strictly defined criteria for administration of steroids due to the retrospective multicenter study design.

In our study, $V_{20}$ was the only dosimetry factor that was significantly associated with pneumonitis in multivariable analysis. Since the $V_{20}$ cut-off value was 18.77% for prediction of grade 2 pneumonitis was much lower than previously reported values, we evaluated the sensitivity and specificity for $V_{20}$ values of 20%, 25%, 30%, and 35%. The specificity increased, but sensitivity was reduced as this value increased. This suggests that severe pneumonitis that is not related to radiotherapy occurs with a constant probability. Other previously suggested criteria, including $V_{10}$ of 30% and 35%, and MLD of 10 Gy, 15 Gy, and 18 Gy, were significant
factors for pneumonitis in univariate analysis; however, these factors are closely correlated with V20.

There are some limitations of the study, including the retrospective design, short follow-up period, and absence of a defined policy to evaluate pneumonitis. The severity of pneumonitis was followed by CTCAE, but diagnosed by each pulmonologist or radiation oncologist. Therefore, the classification of grades 2 and 3 pneumonitis may be ambiguous. Also, in clinical practice, it is difficult to keep V20 at < 19% for bulky NSCLC. Within these limitations, we conclude that the basic concept of radiotherapy with emphasis on V20 is unchanged in CCRT followed by durvalumab, but that an effort to reduce V20 with any modality should be made in use of this therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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