（様式４）

学 位 論 文 の 内 容 の 要 旨

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（学位論文のタイトル）

Kinetics of Prostate-Specific Antigen after Carbon Ion Radiotherapy for Prostate Cancer
（前立腺癌における炭素イオン線治療後のPSA動態）

（学位論文の要旨）2,000字程度、Ａ４判

Background: Radiotherapy has an important role in prostate cancer treatment. Including, Carbon Ion radiotherapy (CIRT) which has potential as a definitive modality for localized prostate cancer. In the surveillance of prostate cancer patients, Prostate-specific antigen (PSA) has become the gold standard biomarker. In curative cases, PSA levels decreased gradually over >5 years post-radiotherapy and eventually reach a nadir. Nevertheless, PSA levels fluctuate and temporarily increase in some patients, this phenomenon is called the PSA bounce. This PSA bounce causes anxiety for prostate cancer patients and clinicians, and may lead to unnecessary salvage treatment in cases that meet the definition of PSA failure. The study about PSA kinetics in prostate cancers is important to differentiate the pattern and characteristic between PSA bounce and PSA failure in each modality. The bounce has been extensively studies in external beam radiotherapy (EBRT) using photon, stereotactic body radiotherapy (SBRT), and high- and low-dose brachytherapy. However, PSA bounce after CIRT has not been examined. **Objective**: This study aimed to elucidate PSA kinetics in prostate cancer patients treated with CIRT. **Population and Method**: We enrolled 131 patients with prostate adenocarcinoma, who meet the following criteria: (i) treated with CIRT at Gunma University Heavy Ion Medical Center, between July 2010 and July 2015; (ii) staged as T1-T3N0M0 according to TNM classification (2002); (iii) no neoadjuvant, adjuvant, or concurrent ADT; and (iv) followed up at least 3 years post-CIRT. Patients treated with CIRT (57.6 Gy relative biological effectiveness (RBE)) in 16 fractions. PSA was measured at 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months post-CIRT. PSA bounce was defined as PSA increase over a cut-off followed by spontaneous decrease to or below the pre-bounce nadir. PSA failure was determined using phoenix criteria (nadir + 2.0 ng/mL). A temporary PSA increased of ≥ 2.0 ng/ml was not classified as failure. **Results**: In our population, we found two distinct patterns for non-failure-associated temporary PSA increased; the classical PSA bounce and PSA surge. PSA surge is a PSA increased at one month, we differentiate this from classical bounce because this pattern has not been reported previously for any radiotherapy modality, and it may have different aetiology. PSA bounce of ≥ 0.2 ng/mL was observed in 55.7% (73/131) of patients. Younger age was a significant predictor for PSA surge. PSA bounce is significant as a favourable prognosis for PSA-failure. Meanwhile, PSA surge, was observed in 67.9% (89/131). In all cases, the surge peaked out quickly and recovered to or below the pre-surge within 2 months. PSA surge amplitude was significantly larger than bounce amplitude (3.39 ± 2.78 ng/mL vs 0.79 ± 1.02 ng/mL). Larger prostate volume was a significant predictor of PSA surge. PSA surge positivity did

not significantly predict PSA failure. **Discussion**: This was the first report of post-treatment PSA kinetics in prostate cancer patients treated with CIRT. PSA bounce was distinguishable from PSA failure, in terms of the timing of occurrence and amplitude (earlier and lower, respectively for the bounce). The data may provide a clinical insight on post-treatment surveillance of CIRT; PSA bounce should be carefully ruled out from failure especially within 36 months post CIRT to prevent unnecessary salvage treatment even when the amplitude exceeds 2.0 ng/mL, whereas a continuous increase in PSA observed after 36 months is more probable for failure than bounce. The Incidence of PSA bounce varies widely among studies, where the various cut-offs employed. When focused on the same cut-off as in our study (i.e., ≥ 0.2 ng/mL), the incidence approximately 25%, 35%, 40%, and 40% for EBRT, SBRT, and high-and low-dose-rate brachytherapy, respectively. In this study, the incidence of PSA bounce for CIRT was 55.7%, which was higher than that reported for other radiotherapy modality. High prevalence of PSA bounce among younger patients was consistent with previous reports on SBRT and brachytherapy. The mechanism underlying PSA bounce and its association with age have not been fully elucidated. However, Yamamoto et al. demonstrated an increase in tumor-infiltrative CD3 and cytotoxic CD8 cells in bounce-positive patients, seemingly explaining the higher incidence of PSA bounce in younger (i.e., more immunocompetent) patients. Predictive significance of PSA bounce with a cutoff of 0.2 ng/mL on favourable PSA failure-free survival was consistent with previous reports on EBRT, and brachytherapy. Differences between PSA surge and bounce in predictive clinical factors and in predictive ability for PSA failure indicate that they are physiologically distinct. Predictive significance of greater prostate volume on higher incidence and no predictive significance on PSA failure indicate that PSA surge may derive from the normal prostate tissues irradiated with carbon ions. Further research is needed to elucidate this issue. **Conclusion**: We demonstrated the post-treatment PSA kinetics in prostate cancer patients treated with CIRT for the first time in a single-institution prospective observational study. PSA bounce can be distinguished from PSA failure in terms of timing of occurrence and amplitude, which will be useful information in the post-treatment surveillance of CIRT.