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学 位 論 文 題 名	Modified Glasgow Prognostic Score is predictive of prognosis for non-small cell lung cancer patients treated with stereotactic body radiation therapy: a retrospective study (体幹部定位放射線治療を行なった非小細胞肺癌患者の修正グラスゴー予後スコアによる予後予測に関する遡及的研究)
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学位論文内容の要旨

Purpose: We aimed to assess the predictive value of the modified Glasgow prognostic score (mGPS) in patients with non-small cell lung cancer (NSCLC) who underwent stereotactic body radiation therapy (SBRT).

Methods: We retrospectively reviewed the records of NSCLC patients who underwent SBRT at our institution from 2001–2016. The original Glasgow prognostic score (GPS) is a 4-point scale that was developed to predict the prognoses of patients receiving chemotherapy for advanced NSCLC. For scoring, one point is added for each of the following criteria: stage IV disease, performance status (PS) score of 2–4, CRP levels >1.0 mg/dL, and albumin levels <3.5 g/dL. The mGPS was developed from the GPS and simplified it by omitting stage and PS. Due to technological advancements, the threshold levels of mGPS were slightly changed. We calculated the mGPS based on a cut-off value of 0.3 mg/dL for CRP and 3.5 mg/dL for albumin. The pretreatment mGPS was calculated and categorized as high (mGPS=1–2) or low (mGPS=0). The associations between the potential prognostic factors and the survival outcomes were assessed using univariate and multivariate Cox proportional hazards models.

Results: The median follow-up duration was 40.7 months. The 5-year overall survival (OS), progression-free survival (PFS), and time to progression (TTP) rates were 44.3%, 36.0%, and 54.4%, respectively. Multivariate analysis revealed that mGPS was independently predictive of OS (hazard ratio [HR] 1.67; 95% confidence interval 1.14–2.44: P = 0.009), PFS (HR 1.58; 1.10–2.28: P = 0.014), and TTP (HR 1.66; 1.03–2.68: P = 0.039). Patients who had high mGPS showed significantly worse OS (33.3 vs. 64.5 months, P=0.003) and worse PFS (23.8 vs. 39.0 months, P=0.008) than those who had low mGPS. The data showed a trend that patients with high mGPS suffered earlier progression compared with those with low mGPS (54.3 vs. 88.1 months, P=0.149).

Discussion: Limited studies have been done to assess the prognostic value of the mGPS in NSCLC patients treated with SBRT. Our results show that a high mGPS might serve as a prognostic factor to detect patients who could suffer from early disease progression. Recent studies have elucidated the mechanisms by which systemic inflammation negatively influences survival. Inflammation can be triggered by infectious or non-infectious agents. The release of pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), plays a key role in dissociation of nuclear factor kappa B (NF-kB) from its inhibitors. NF-kB can induce an increase in IL-6 production, which results in the release of acute-phase reactants including CRP. Conversely, albumin levels are reduced during chronic inflammation owing to increased vascular permeability and decreased hepatic albumin synthesis. The mGPS, which is a combination of serum CRP and albumin levels, might serve as an indicator of chronic inflammation and malnutrition, which result in a worse prognosis. We recommended that patients who have a high mGPS should be considered for adjuvant intensive systemic therapies, if tolerable. A combination of SBRT and immunotherapy seems to be a promising option, which has shown positive results in locally advanced and metastatic NSCLC.

Conclusion: This study evaluated the largest number of cases for the relationship between the mGPS and survival-related outcomes in NSCLC patients treated with SBRT. We confirmed that mGPS is independently predictive of prognosis in NSCLC patients treated with SBRT.

論文審査結果の要旨

早期の非小細胞性肺がんに対する外科手術が困難な症例に対して、定位放射線治療の局所治療成績はすでに確立しているといえる。しかしながらもともと全身状態の芳しくない症例も含まれているため長期予後の問題や照射野外の領域での再発は一定数存在し、その改善は課題となっている。グラスゴー予後スコアは血清アルブミンレベルと CRP 値によりスコア付けをして治療前の栄養状態を評価し、がんの予後を予測するモデルである。原法に対して CRP のカットオフ値が変更され、修正グラスゴー予後スコアが汎用されている。最初はがんに対する化学療法の予後を予測するために開発されたが、現在は外科治療においても活用されている。そこで本研究ではこの修正グラスゴー予後スコアを非小細胞性肺がんに対する定位放射線治療に応用し、多変量解析を用いて予後予測成績を評価した。その結果、全死亡と無増悪生存期間では修正グラスゴー予後スコアの高い群において予後が不良であった。これより非小細胞性肺がんに対する定位放射線治療の遠隔成績の予測に有効であることが示された。本研究の臨床におけるインパクトは大きく、治療方針の検討、治療後のフォローについて患者ごとに最適な対応策を得るための強力なツールとなる可能性を秘めていると言える。これらの点で学術的にも臨床的にも意義深い研究成果と考えられる。

研究方法及びデータの信頼性については、統計学的な処理も含めて何ら問題ないと考える。今回の研究結果はすでに英文論文にまとめられ Journal of Radiation Research に掲載されており、医学博士論文としての質を十分に満たしていると評価できる。