# The Prognostic Value of Quantitative $^{11}$C-Methionine PET Imaging in Patients with Carcinoma of the Uterine Cervix Treated With Carbon Ion Radiotherapy

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**Abstract: Objective:** It is to evaluate the prognostic value of the change in tumor uptake of $^{11}$C-methionine (MET) before and after carbon ion radiotherapy (CIRT) in patients with carcinoma of the uterine cervix and its correlation with clinical factors such as survival, local control and metastatic rates. **Methods:** Forty one cases with cancer cervix with both pre- and post-CIRT PET imaging using $^{11}$C-methionine were retrospectively analyzed. Assessment of the change in tumor uptake of MET before and after CIRT was performed in all cases with the semiquantitative tumor-to-non-tumor ratio (T/N ratio). Kaplan-Meier test was used to analyze the relationship and statistical significance between various factors. **Results:** The overall mean survival time was 41.9 months. Significantly better survival ($p$=0.0046) was detected in patients with post-CIRT reduction of MET uptake of ≥ 39.2% than in patients with percent reduction of < 39.2% (2 year survival rate was 60.6% versus 37.5% respectively). Patients with baseline T/N ratio of ≤ 14.7 had a significantly lower metastatic rate than patients with baseline T/N ratio of > 14.7 ($p$ <0.0001). Patients with post-CIRT T/N ratio of ≤ 7.6 had a significantly lower local recurrence rate than patients with post-CIRT T/N ratio of > 7.6 ($p$ <0.0001). **Conclusions:** The change in MET uptake before and after CIRT as measured by T/N ratio was an independent predictor of survival in patients with carcinoma of the uterine cervix treated by CIRT. Additional potential value was found for the prediction of metastatic and local control rates with baseline and post-CIRT T/N ratio respectively.

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**Key words:** C-11 Methionine PET, cervical cancer, CIRT, T/N ratio.

## 1.Introduction:

Cervical cancer represents an important global public health problem and is accounted as the second most common neoplasia among women worldwide (1). Its incidence is higher in developing than developed countries by about four fifth of the global burden, and it is a major cause of death in women in their reproductive period, in Asia, Africa and Latin America (2).

The reported survival rates showed marked variation among countries because of differences in clinical stage at presentation and the level of cancer-related health services available in different countries. The five-year survival rate range from less than 25% (as in black patients of Uganda and Zimbabwe) to 75% in developed countries (3-6).

The estimated age-adjusted cancer mortality rates for cancer cervix ranged between 3 and 8 per 100,000 women in most developed countries and 10–25 per 100,000 women in most developing countries (1).

**Radiation therapy for cervical cancer:**

Many different advanced modalities are currently used in radiation oncology such as stereotactic radiotherapy, radiosurgery, intensity- modulated radiotherapy (IMRT) and three-dimensional planning of brachytherapy, and can deliver radiation dose with high geometric precision (7).

Also, several reports have demonstrated the favorable results of carbon ion beam radiotherapy (CIRT) in the treatment of different malignant tumors (8-9), and as regard of cervical cancer, several studies have reported CIRT as a feasible method for therapy of cervical cancer patients with high local control rate and favorable disease free survival (10 – 12).

In Japan, cancer treatment by heavy charged particle radiation therapy was initiated at the National Institute of Radiological Sciences in Chiba in June, 1994, using carbon ions generated by heavy-ion medical accelerator in Chiba (HIMAC, Chiba, Japan) (13).

**Disease evaluation:**

Computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are current imaging technology for evaluation of cervical cancer. Both CT and MRI have similar efficacy in evaluating cervical volume and lymph node status, excluding obstructive uropathy, and identifying metastatic disease (14, 15).

Positron Emission Tomography (PET), being able to measures metabolic activity, is more sensitive

in predicting nodal involvement and is useful as a follow-up tool of response to chemoradiation and recurrence identification (16, 17). Flourine-18 fluorodeoxyglucose (F-18 FDG) is the tracer being most commonly used in PET imaging for the evaluation of gynecologic cancer, (18). Several studies in cancers of the head and neck, lung, and esophagus reported a prognostic role of FDG uptake in the primary tumor where standardized uptake value (SUV) greater than the median, was a predictive of a worse outcome and a shorter disease-free survival. (19-20). Other potentially useful PET traces used in gynecologic cancer include $^{11}$C-acetate (for fatty acid metabolism in tumor cells) (21), $^{11}$C-choline (for choline metabolism in tumor cells) (22), O-(2-[$^{18}$F]fluoroethyl)-L-tyrosine ($^{18}$F FET) (for brain tumor identification) (23) and [$^{18}$F]fluoromisonidazole and Cu-labeled diacetyl-bis(N(4)-methylthiosemicarbazone) (for tumor hypoxia status) (24).

L-methionine is an essential amino acid which plays a central role in the altered metabolism of cancer cells (25), and C-11 methionine (MET) has been used for imaging in oncology since its increased uptake, as measured by PET, has been suggested to reflect increased transport, transmethylation rate, and protein synthesis of malignant tissue (26). The degree of MET uptake also is correlated with the amount of viable tumor tissue, (27) and MET-PET imaging could allow for targeting the tumor tissue with the highest metabolic activity (28).

Data from preclinical studies on the use of MET for the evaluation of chemo- or radiotherapy generally show that its uptake is reduced more rapidly than F-18 FDG after therapy, and has less influence of radiation-induced inflammatory reaction after radiotherapy (29-31).

To our knowledge, no previous study has evaluated the value of the semi-quantitative T/N ratio of C-11 MET PET imaging as a prognostic factor for cancer cervix after CIRT.

**2.Patients and methods:**

Patients eligible for the study had histologically confirmed cervical cancer. Tumors were judged to be unresectable by the referring surgeon, or the patients were medically inoperable or declined surgery. All patients included had both pre- and post-CIRT MET PET studies. Patients with prior radiation therapy to the same site or who had received chemotherapy (within 4 weeks) before CIRT treatment were excluded from the study. Patients without either pre or post-CIRT MET PET were excluded from the study. All patients included in the study had signed the informed consent form approved by the Institutional Review Board for both the treatment and PET imaging studies.

**Patients and tumor characteristics:**

Table 1 presents the patient characteristics and MET PET results. A total of 41 patients were included with a mean follow-up of 40.8 months (range, 4.7 – 136.7). At the end of the study, 20 patients had died. The mean age was 61.07 ± 12.4 SD (range, 33-86). In this study, squamous cell carcinoma was the most common type of cervical carcinoma and found in 25 patients (61%) followed by adenocarcinoma in 15 patients (36.6%) and one case of adenosquamous carcinoma (2.4%).

**PET Imaging:**

C-11 methionine was prepared by a method modified from the synthesis of Langstorm et al (32). Whole-body PET scanners (ECAT EXACT HR+ and ECAT EXACT 47; Siemens CTI, Knoxville, Tenn.) were used providing an axial field of view of 15.5 and 16.2 cm, resulting in 63 and 47 transverse slices with a thickness of 2.5 and 3.4 mm, respectively. Transmission scans were performed with germanium-68 rod sources. Emission data corrected for random events, dead time and attenuation were reconstructed by filtered backprojection using a Ramp filter with a cutoff frequency of 0.4 followed by the decay correction.

Patients fasted for at least 4 h before PET imaging. Before MET injection, all of the patients underwent transmission scan for one (ECAT EXACT HR+) or two bed positions (ECAT EXACT 47) including lesion site, each bed position for 20 and 10 min for ECAT EXACT HR+ and ECAT EXACT 47, respectively. Static emission data for the same positions were obtained from 23 min after IV administration of ~ 740 MBq MET (the mean dose of $^{11}$C -methionine in the baseline scan was 18.9 mCi ± 1.3 (699.3 MBq ± 48.1 MBq) and for post-CIRT scan was 18.8 mCi ± 2.4 (695.6 ± 88.8 MBq). For the difference in sensitivity in PET scanners, static emission scans were performed for 30 min in ECAT EXACT HR+ and 15 min in ECAT EXACT 47 for each bed position respectively. The mean period for MET scan after completion of carbon ion radiotherapy was 27.2 ± 11.4 days.

**Analysis of PET mages:**

The area with the maximum MET uptake was detected in the transaxial slices of PET images for both baseline and post-CIRT studies. The areas with maximum MET uptake are thought to reflect the most metabolically active area of the tumor and hence the regions with more aggressive tumor. The choice of these areas for analysis was based on the inherent assumption that the overall behavior of the tumor is predicted by the activity of its most active regions. To quantitatively evaluate tumor behavior, region of interest (ROI) with a diameter of 1 cm was manually drawn over the area with maximum MET uptake, and

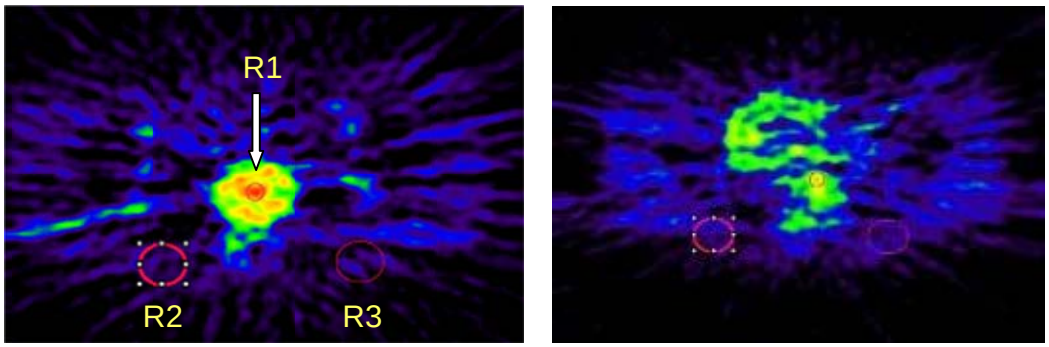
ROIs of larger diameter were drawn on the homologous contralateral or surrounding normal tissue for the background radioactivity measurement.

Tumor-to-nontumor ratio (T/N ratio) was calculated using the formula: T/N ratio = mean counts per pixel of tumor regions of interest/mean counts per pixel of normal tissue regions of interest, figure 1.

**Table 1:** Patient characteristics and MET PET results (n = 41 patients).

| Patient no. | Age (Years) | Histopathology | TNM | Radiation dose (GyE) | Dose fractionation | Dose per fractionation | Pre-CIRT T/N ratio | Post-CIRT T/N ratio | Survival (months) | Uptake ratio | Local recurrence | Distant metastasis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 61 | Adenocarcinoma | T3bN0M0 | 68 | 20 | 3.0 | 7.1 | 5.3 | 39.3 | 74.6 | No | Yes |
| 2 | 43 | S.C.C | T3N0M0 | 64 | 20 | 3.0 | 6.5 | 3.3 | 12.1 | 50.8 | Yes | No |
| 3 | 47 | S.C.C | T3bN1M0 | 64 | 20 | 3.0 | 11.9 | 4.2 | 22.6 | 35.3 | No | Yes |
| 4 | 75 | Adenocarcinoma | T4N0M0 | 68 | 20 | 3.0 | 4.6 | 4.2 | 26.4 | 91.3 | No | Yes |
| 5 | 81 | Adenocarcinoma | T3bN0M0 | 68 | 20 | 3.0 | 7.0 | 2.5 | 34.9 | 35.7 | No | No |
| 6 | 68 | Adenocarcinoma | T3bN1M0 | 71 | 20 | 3.0 | 7.8 | 2.9 | 38.6 | 37.2 | No | Yes |
| 7 | 69 | S.C.C | T3bN0M0 | 72 | 20 | 3.0 | 6.0 | 2.8 | 35.6 | 46.7 | No | No |
| 8 | 72 | Adenocarcinoma | T3bN0M0 | 71 | 20 | 3.0 | 6.3 | 2.9 | 17.3 | 46.0 | Yes | Yes |
| 9 | 76 | S.C.C | T3bN1M0 | 72 | 20 | 3.0 | 13.5 | 3.2 | 23.0 | 23.7 | No | No |
| 10 | 56 | Adenocarcinoma | T3bN0M0 | 71 | 20 | 3.0 | 9.6 | 3.8 | 44.6 | 39.6 | No | Yes |
| 11 | 71 | Adenocarcinoma | T3bN0M0 | 65 | 20 | 3.0 | 7.2 | 2.8 | 58.4 | 38.9 | No | No |
| 12 | 50 | Adenocarcinoma | T2bN0M0 | 68 | 20 | 3.0 | 6.8 | 4.9 | 23.7 | 72.1 | No | Yes |
| 13 | 67 | Adenocarcinoma | T2bN1M0 | 68 | 20 | 3.0 | 9.6 | 4.0 | 56.5 | 41.7 | Yes | No |
| 14 | 55 | Adenosquamous carcinoma | T4N1M0 | 68 | 20 | 3.0 | 4.8 | 6.6 | 46.9 | 137.5 | Yes | No |
| 15 | 43 | S.C.C | T3bN0M0 | 68 | 20 | 3.0 | 5.8 | 2.3 | 22.1 | 39.7 | Yes | Yes |
| 16 | 52 | S.C.C | T3bN0M0 | 72 | 20 | 3.0 | 8.5 | 4.7 | 34.8 | 55.3 | No | No |
| 17 | 54 | S.C.C | T3bN0M0 | 72 | 20 | 3.0 | 8.8 | 2.5 | 19.1 | 28.4 | No | No |
| 18 | 48 | Adenocarcinoma | T4N1M0 | 71 | 20 | 3.0 | 3.8 | 3.1 | 6.5 | 81.6 | No | No |
| 19 | 63 | S.C.C | T2bN1M0 | 71 | 20 | 3.0 | 7.6 | 3.0 | 4.7 | 39.5 | No | No |
| 20 | 33 | S.C.C | T4N1M0 | 64 | 20 | 3.0 | 14.7 | 4.6 | 21.1 | 31.3 | No | Yes |
| 21 | 86 | S.C.C | T3bN1M0 | 73 | 24 | 3.0 | 13.9 | 5.4 | 106.8 | 38.8 | No | No |
| 22 | 81 | S.C.C | T3bN0M0 | 69 | 24 | 2.9 | 13.2 | 5.2 | 85.8 | 39.4 | No | Yes |
| 23 | 62 | S.C.C | T4NXM0 | 62 | 24 | 2.6 | 11.5 | 6.2 | 109.0 | 53.9 | No | No |
| 24 | 74 | S.C.C | T3bN1M0 | 53 | 24 | 2.2 | 9.7 | 5.9 | 26.1 | 60.8 | Yes | No |
| 25 | 76 | S.C.C | T3bN0M0 | 67 | 24 | 2.8 | 6.2 | 3.1 | 94.3 | 50.0 | No | No |
| 26 | 50 | Adenocarcinoma | T4N1M0 | 72 | 24 | 3.0 | 7.9 | 4.8 | 8.5 | 60.8 | No | Yes |
| 27 | 57 | S.C.C | T3bN0M0 | 73 | 24 | 3.0 | 8.4 | 4.9 | 85.2 | 58.3 | Yes | No |
| 28 | 56 | S.C.C | T3bN1M0 | 62 | 24 | 2.6 | 20.9 | 5.1 | 13.2 | 24.4 | No | Yes |
| 29 | 74 | S.C.C | T4N1M0 | 73 | 24 | 3.0 | 7.4 | 2.6 | 105.1 | 35.1 | No | No |
| 30 | 43 | Adenocarcinoma | T2bN0M0 | 68 | 20 | 3.0 | 10.5 | 6.2 | 16.8 | 59.0 | Yes | No |
| 31 | 46 | Adenocarcinoma | T4N1M0 | 66 | 20 | 3.3 | 11.7 | 6.3 | 25.1 | 53.8 | No | Yes |
| 32 | 60 | S.C.C | T3bN1M0 | 53 | 16 | 3.3 | 11.6 | 1.8 | 120.6 | 15.5 | No | Yes |
| 33 | 52 | S.C.C | T3bN1M0 | 73 | 24 | 3.0 | 6.5 | 3.0 | 24.6 | 46.2 | No | Yes |
| 34 | 63 | S.C.C | T4N0M0 | 69 | 24 | 2.9 | 6.4 | 3.3 | 26.7 | 51.6 | No | Yes |
| 35 | 62 | Adenocarcinoma | T3bNXM0 | 53 | 24 | 2.2 | 17.2 | 5.0 | 9.9 | 29.1 | No | Yes |
| 36 | 60 | S.C.C | T3bNXM0 | 58 | 24 | 2.4 | 12.3 | 4.9 | 136.7 | 39.8 | No | No |
| 37 | 73 | S.C.C | T3bNXM0 | 72 | 24 | 3.0 | 11.7 | 7.6 | 8.7 | 65.0 | No | Yes |
| 38 | 55 | S.C.C | T3bN1M0 | 69 | 24 | 2.9 | 7.9 | 2.4 | 23.1 | 30.4 | No | Yes |
| 39 | 77 | S.C.C | T3bNXM0 | 53 | 24 | 2.2 | 11.7 | 3.0 | 70.3 | 25.6 | No | No |
| 40 | 54 | S.C.C | T3bN1M0 | 62 | 24 | 2.6 | 13.3 | 10.7 | 20.3 | 80.5 | Yes | Yes |
| 41 | 59 | Adenocarcinoma | T3bN1M0 | 62 | 20 | 3.0 | 7.3 | 10.6 | 13.6 | 145.2 | Yes | No |

$$\text{Tumor-to-normal tissue-ratio (T/N ratio)} = \frac{R1}{(R2 + R3) / 2} \times 100.$$




(a) (b)

***Figure 1; calculation of T/N ratio (a) Pre-therapy scan (transverse cut) (b) Post-therapy scan (transverse cut).***

Where R1 is about 1 cm ROI on the tumor site with the most intense uptake, while R2 & R3 are larger diameter ROI at normal soft tissue background.

$$\text{The uptake ratio was calculated from the formula: Uptake ratio} = \frac{\text{Post-CIRT T/N ratio}}{\text{Pre-CIRT T/N ratio}} \times 100.$$

**Statistical analysis:**

Kaplan-Meier test was used to analyze the relationship and statistical significance between various factors. Survival time was defined as the time interval from initiation of carbon ion radiotherapy until death or last follow up date. A difference with $P < 0.05$ was considered significant.

**3.Results:**

Generally, high degree of MET uptake was observed in baseline studies of all primary tumors. The mean baseline (pre-CIRT) T/N ratio was 9.39 ± 3.59 (range, 3.8 – 20.9). All patients had a second MET PET study within two months after CIRT. The size of the area of MET accumulation visibly decreased in all tumor sites while the intensity of uptake markedly decreased in 39 out of the 41 tumors (95.1%). After CIRT, the mean T/N ratio decreased significantly ($P$ =0.000) to 4.43 ± 1.99 (range, 1.8 – 10.7).

In two out of the 41 cases (4.9%), there was actually increased, instead of decreased, T/N ratio. One case was adenosquamous carcinoma (T4N1M0) and showed Pre-CIRT T/N ratio of 4.8 and post-CIRT T/N ratio of 6.6. The other case was adenocarcinoma (T3BN1M0) and showed pre-CIRT T/N ratio of 7.3 and post-CIRT T/N ratio of 10.6. Both cases showed local recurrence on follow up.

The overall mean survival time was 41.9 months. Significantly better survival ($P$ =0.0046) was detected in patients with uptake ratio <60.8% (denoting post-CIRT reduction of MET uptake of ≥ 39.2%) than in patients with percent reduction of < 39.2% (2 year survival rate was 60.6% versus 37.5% respectively), figure 2.

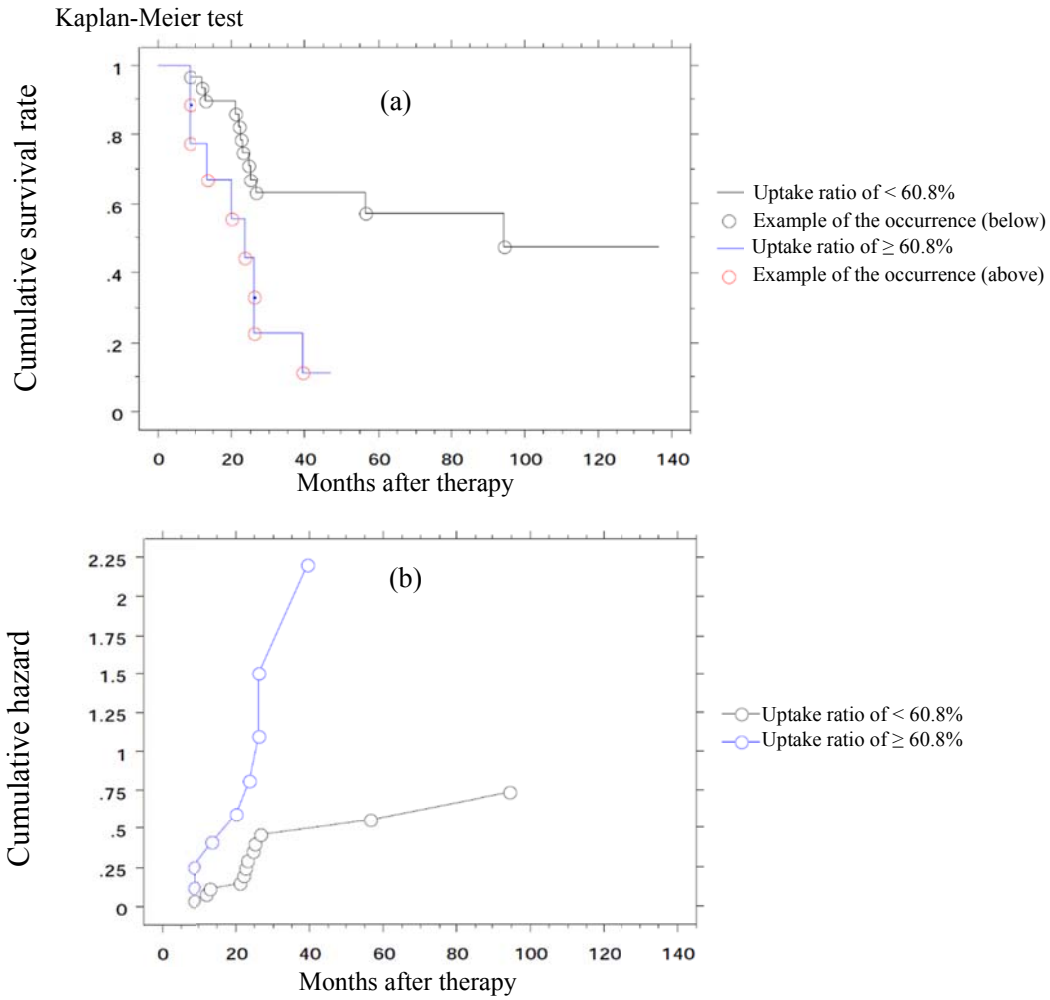



**Figure 2. (a) Overall survival according to uptake ratio (P=0.0046). (b) Cumulative hazard by uptake ratio.**

Also, significantly better survival (*P* <0.0001) was found in patients with baseline T/N ratio of ≤ 14.7 and in patients with post-CIRT T/N ratio of ≤ 7.6 than in patients with baseline T/N ratio of > 14.7 and patients with post-CIRT T/N ratio of > 7.6 respectively.

Twenty one out of 41 cases (51.2%) had no metastasis on follow up, while 20 cases (48.8%) developed metastasis during the follow up period. It the current study, patients with baseline T/N ratio of ≤ 14.7 had a significantly lower metastatic rate than patients with baseline T/N ratio of > 14.7 (*P* <0.0001). Figure 3 show metastasis free survival and cumulative hazard for metastasis by Pre-CIRT MET T/N ratio.

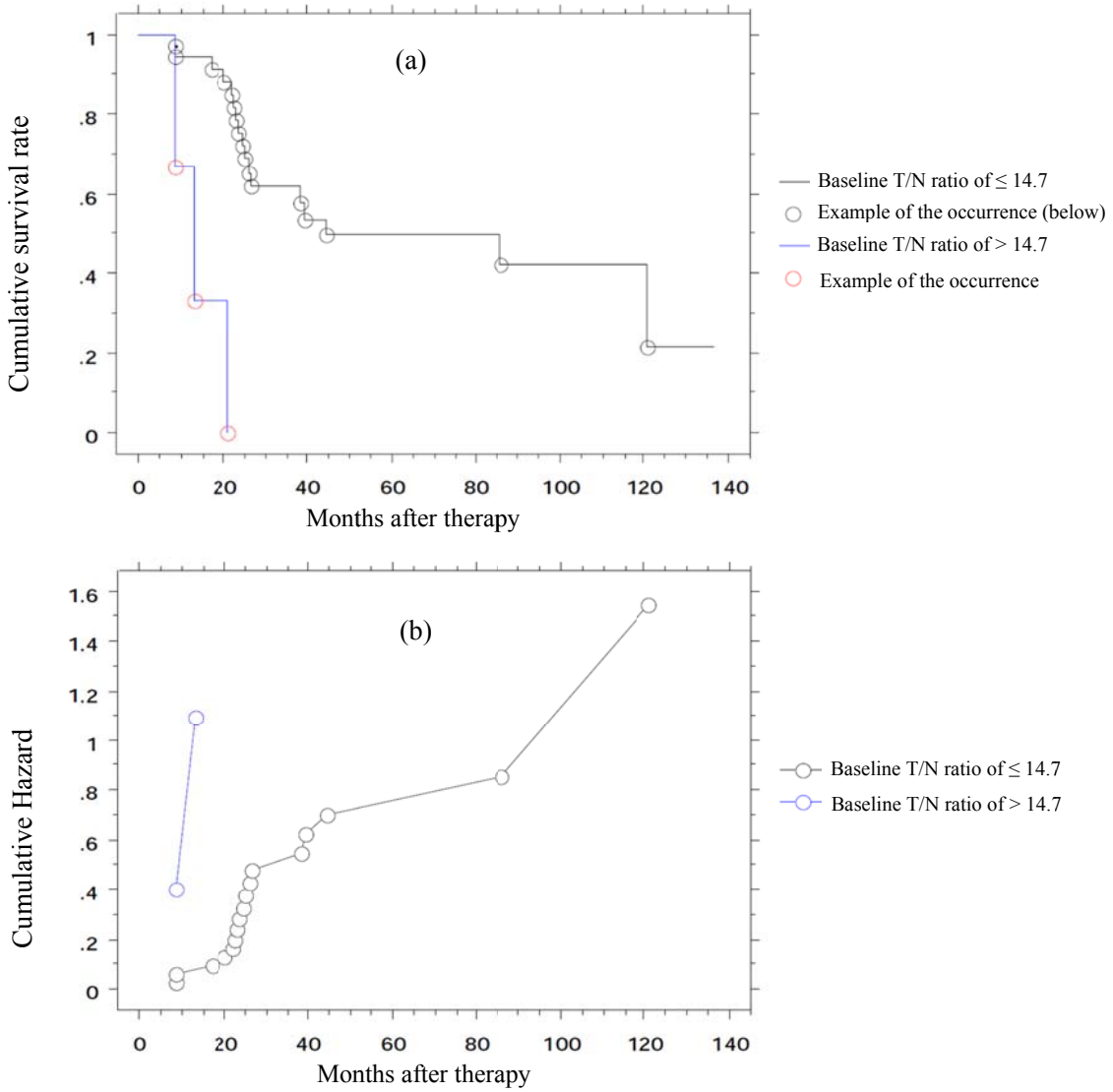



**Figure 3. (a) Metastasis free survival according to Pre-CIRT T/N ratio (P<0.0001). (b) Cumulative hazard for metastasis by Pre-CIRT MET T/N ratio.**

Also, significantly less metastatic rate was found in patients with uptake ratio of < 60.8% and in patients with post-CIRT T/N ratio of < 7.6 than in patients with uptake ratio ≥ 60.8% and patients with post-CIRT T/N ratio of > 7.6 ($P$ = 0.0285 & $P$ <0.0042 respectively).

Thirty one patients (75.6%) had no local recurrence on follow up while 10 patients (24.4%) developed recurrence. Our study results showed that; patients with post-CIRT T/N ratio of ≤ 7.6 had a significantly lower local recurrence rate than patients with post-CIRT T/N ratio of > 7.6 ($P$ <0.0001). Figure 4 show recurrence free survival and cumulative hazard for recurrence according to Post-CIRT T/N ratio.

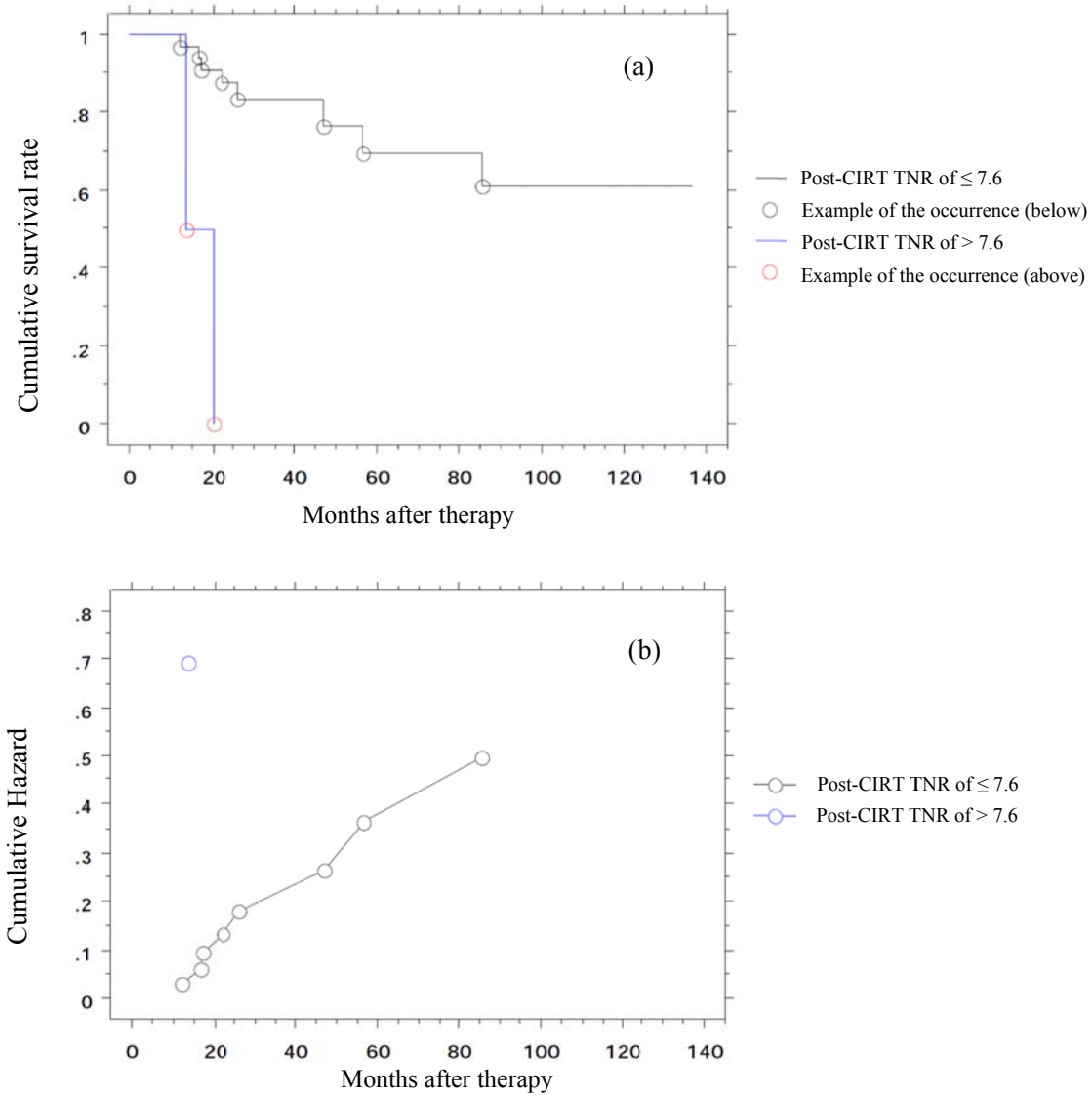



**Figure 4. (a) Recurrence free survival according to Post-CIRT T/N ratio (P<0.0001). (b) Cumulative hazard for recurrence by Post-CIRT MET T/N ratio.**

Also significantly lower local recurrence rate was found in patients with uptake ratio of < 59% and in patients with pre-CIRT T/N ratio of < 11.5 than in patients with uptake ratio of ≥ 59% and patients with pre-CIRT T/N ratio of > 11.5 ($P$ <0.0015 & $P$ <0.048 respectively).

**4.Discussion:**

There are several traditional prognostic factors influencing survival in cervical cancer patients have been established. Some of these factors are related to patients' characteristics (e.g., age, blood hemoglobin level), the others being related to tumor (e.g., stage, lymph node involvement, size of tumor) or treatment characteristics (e.g., irradiation doses, duration treatment) (33). However, Harry *et al.,* (34) reported that traditional prognostic factors as tumor size, grade, and stage are not ideal for predicting patient outcome. In addition, the detection of chemosensitivity or resistance via the use of in vitro assays has not yet translated into routine clinical practice and biomarkers and tumor markers vary in their predictive ability. Imaging techniques, particularly those with the ability to characterize biological tissues and provide functional, structural, and molecular information, have the potential to noninvasively integrate physical and metabolic

information attempting to evaluate and predict therapy response and so influence clinical outcome.

For all cancer types, tumor response to therapy is considered a significant prognostic factor and is relevant for the primary tumor, metastatic disease and recurrent disease (35). For evaluation of the response to therapy of the primary tumor, CT and MRI are considered nonspecific tests and are only informative if they reveal an increase in size, which implies tumor growth (36).

Functional FDG PET imaging is now considered a standard pretreatment investigation for staging of many cancers. Post-therapy FDG-PET has been utilized to monitor tumor response to therapy in several tumors (35). Also, many studies have demonstrated the value of FDG PET imaging in identifying lymph node involvement, distant metastasis and local recurrence in cervical cancer patients (37, 38). Kidd *et al.,* 2007 concluded that the SUVmax of the cervical tumor at diagnosis is a sensitive biomarker of treatment response and prognosis for patients with cervical cancer (20).

Similarly, imaging with MET PET has been found recently to be feasible for the evaluation of treatment effects after medical therapy. In a large series of pituitary adenomas and in some meningiomas, a decrease in the uptake of MET has been shown to represent a positive treatment effect (39). MET PET has also been found to provide valuable information in assessing the effect of chemotherapy earlier than other methods (40, 41), in assessment of effect of combined radiochemotherapy treatment in patients with inconclusive CT findings (42, 43), and in differentiation between viable residual tumor mass from post-radiotherapy tissue changes (44). All these data indicate an evident relationship between tumor aggressiveness and MET uptake, which in turns reflects its prognostic value (45). Therefore, in our study, we tried to investigate the value of quantitative MET PET in predicting the outcome in patients with cervical cancer treated by CIRT.

In Kidd *et al.,* 2007 study for assessment of the value of SUVmax of F-18 FDG in predicting treatment response and prognosis of cervical cancer patients after therapy, the highest survival rate was found in patients with pre-therapy SUVmax of ≤5.2 (20). In our study, significantly better survival rate was found in patients with pre-CIRT T/N ratio of ≤ 14.7 ($P$<0.0001).

Zhang *et al.,* (45) in their study for the evaluation of CIRT outcome in patients with bone and soft tissue sarcomas, reported significantly better survival in patients with baseline MET uptake T/N ratio of ≤6 and post-CIRT MET uptake T/N ratio of ≤4.4 than in patients with larger T/N ratios. In our study, patients with a pre-CIRT T/N ratio of ≤ 14.7 and patients with post-CIRT T/N ratio of ≤ 7.6 had significantly better survival ($P$<0.0001) than patients with pre-CIRT T/N ratio of > 14.7 and patients with post-CIRT T/N ratio of >7.6 respectively.

In addition, significantly better survival was found also in patients with post-CIRT reduction of MET uptake of ≥ 39.2% than in patients with post-CIRT MET percent reduction of < 39.2% respectively, ($P$=0.0046). This figure was similar to that reported by Zhang et al 2004, where they found that patients with a reduction of MET uptake >30% showed a better survival than patients with a reduction ≤30%.

It can be expected that the different pathology of the primary tumor is responsible for the different values of pre-and post-CIRT T/N ratio between our study and the study of Zhang. On the other hand, the significant cutoff value of the uptake ratio in both studies was very close (39.2% in our study versus 30% in their study) supporting the reliability of the quantitative MET PET analysis.

The results of Zhang *et al.,* (45) study had not found a significant correlation in the post-CIRT uptake between patients with and without recurrence, however, in our study, the most significant correlation regarding the recurrence rate was found in relation to post-CIRT of <7.6 (P<0.0001), however, this can be attributed to variable uptake characteristics among different tumors. In addition, the most significant correlation ($P$<0.0001) regarding overall survival in our study was found in relation to pre-CIRT T/N ratio of ≤14.7 and post-CIRT T/N ratio of <7.6, while the most significant correlation regarding metastasis free survival was found in relation to pre-CIRT of ≤14.7.

A reported relative limitation for the early use of FDG PET in assessing the response to radiation therapy is the possibility of its high uptake in inflammatory lesions which may results in false positive results (46). Schwarz *et al.,* 2009 on his article for exploration of the use of $^{18}$F-FDG PET in monitoring treatment response in cancer of the cervix and ovaries, reported that 18F-FDG PET can provide reliable long-term prognostic information only 3 mo after the completion of therapy (47). In literature, MET uptake has been reported to correlate better than FDG with tumor proliferative activity in squamous cell head and neck cancer cell lines (48). In addition, it is reported that no significant MET uptake occurs in chronic inflammatory or radiogenic lesions (29-31, 49). In our study, the post-CIRT MET PET study was performed within 2 months after CIRT (mean=27.2 ± 11.4 days) with 32 out of the 41 patients (78%) performed their post-CIRT scan within one month. So, our study results indicate the feasible use of MET

PET early post therapy to provide reliable prognostic data about overall survival, tumor response, and assessment of possibility of recurrence or metastasis.

**Conclusion:**

The difference in tumor MET uptake as evaluated by the semi-quantitative T/N ratio provided information regarding multiple prognostic factors as overall survival, recurrence and metastatic events. Different quantitative parameters as pre-CIRT T/N ratio, post-CIRT T/N ratio and the difference in uptake ratio were all independent predictors for survival, recurrence and metastatic events in patients with cervical cancer. Hence, quantitative MET PET can be a valuable tool in early evaluation of therapeutic options in treatment planning, in monitoring the effect of therapy, and in perdition of disease outcome.

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**Abbreviations:**

$^{11}$C-methionine (MET) Carbon ion radiotherapy (CIRT) Tumor-to-nontumor ratio (T/N ratio) Intensity- modulated radiotherapy (IMRT) Heavy-ion medical accelerator in Chiba (HIMAC)

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