The Dosimetric and Temporal Effects of Respiratory-Gated, High-Dose-Rate Radiation Therapy in Patients With Lung Cancer

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Abstract
Purpose: To evaluate the dosimetric and temporal effects of high-dose-rate respiratory-gated radiation therapy in patients with lung cancer. Methods: Treatment plans from 5 patients with lung cancer (3 nongated and 2 gated at 80EX-80IN) were retrospectively evaluated. Prescription dose for these patients varied from 8 to 18 Gy/fraction with 3 to 5 treatment fractions. Using the same treatment planning criteria, 4 new treatment plans, corresponding to 4 gating windows (20EX-20IN, 40EX-40IN, 60EX-60IN, and 80EX-80IN), were generated for each patient. Mean tumor dose, mean lung dose, and lung V20 were used to assess the dosimetric effects. A MATLAB algorithm was developed to compute treatment time. Results: Mean lung dose and lung V20 were on average reduced between -16.1% to -6.0% and -20.0% to -7.2%, respectively, for gated plans when compared to the corresponding nongated plans, and between -5.8% to -4.2% and -7.0% to -5.4%, respectively, for plans with smaller gating windows when compared to the corresponding plans gated at 80EX-80IN. Treatment delivery times of gated plans using high-dose rate were reduced on average between -19.7% (-0.10 min/100 MU) and -27.2% (-0.13 min/100 MU) for original nongated plans and -15.6% (-0.15 min/100 MU) and -20.3% (-0.19 min/100 MU) for original 80EX-80IN-gated plans. Conclusion: Respiratory-gated radiation therapy in patients with lung cancer can reduce lung dose while maintaining tumor dose. Because treatment delivery during gated therapy is discontinuous, total treatment time may be prolonged. However, this increase in treatment time can be offset by increasing the dose delivery rate. Estimation of treatment time may be helpful in selecting patients for respiratory gating and choosing appropriate gating windows.

Keywords
4DCT, 4D dose, gating, gated radiation therapy, treatment time

Abbreviations
CT, computed tomography; 4DCT, 4-dimensional computed tomography; GTV, gross tumor volume; IMRT, intensity-modulated radiation therapy; ITV, internal target volume; MLD, mean lung dose; MTD, mean tumor dose; PTV, planning target volumes; RGRT, respiratory-gated radiation therapy; SBRT, stereotactic body radiation therapy; TPS, treatment planning system; VMAT, volumetric modulated arc therapy.

Introduction
When treating lung tumors with radiation therapy, respiration-induced tumor motion can yield large uncertainties in target delineation and localization.1-6 In an effort to characterize and reduce the impact of this motion, various techniques have been presented, including respiratory-gated techniques, breath-hold techniques, forced shallow breathing methods, and real-time tumor tracking methods.7-9

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Table 1. Summary of Patient Characteristics.

| Patient | Lung Volume, cm³ | PTV Volume, cm³ | Max Tumor Motion, mm | Prescription Dose, Gy | Treatment | Gated Therapy |
|---------|------------------|-----------------|---------------------|----------------------|-----------|--------------|
| P1      | 816              | 14              | 6                   | 50                   | SBRT      | Yes          |
| P6      | 1859             | 110             | 8                   | 40                   | SBRT      | No           |
| P7      | 1502             | 33              | 10                  | 54                   | SBRT      | No           |
| P8      | 1018             | 115             | 12                  | 61.2                 | IMRT      | Yes          |
| P9      | 1695             | 141             | 10                  | 40                   | SBRT      | No           |

Abbreviations: IMRT, intensity-modulated radiation therapy; PTV, planning target volume; SBRT, stereotactic body radiation therapy.

Respiratory-gated radiation therapy (RGRT) involves monitoring the respiratory signal and only delivering radiation when the patient is within a specific window of the respiratory cycle, thereby reducing the size of the target volume and increasing the amount of normal tissue spared. Several recent studies using 4-dimensional computed tomography (4DCT) have shown that the use of patient-specific treatment margins and respiratory gating, rather than standard population-based treatment margins, can reduce normal tissue toxicity.\(^8\)\(^-\)\(^12\) However, some have pointed out that the additional dosimetric benefits from respiratory gating may be modest and not justify the challenges of RGRT, including the increased time for treatment delivery and, consequently, the increased potential for uncertainty introduced from patient movement.\(^11\)\(^-\)\(^13\) While increased treatment delivery time may not be of great concern for cases which only require a few minutes to complete, as may be true for some treatment plans using volumetric modulated arc therapy (VMAT), cases requiring longer treatment times, such as those using step-and-shoot intensity-modulated radiotherapy (IMRT), may benefit from the ability to estimate treatment time when assessing potential gating windows. Currently, no established guidelines concerning the use of respiratory gating have been defined.\(^3\)\(^,\)\(^13\)

Treatment delivery during gated therapy is not continuous, and as a result, total treatment time is prolonged due to the decreased duty cycle (ie, percentage of the beam-on time). Although various gating methods have been suggested, a limited number of publications were found to report on treatment times for gated radiation therapy.\(^14\)\(^-\)\(^16\) One common method for reducing gated treatment times involves the use of breath hold during treatment delivery. Berson et al\(^14\) compared gated therapy using breath-hold coaching versus free breathing without coaching and found that treatment times decreased from 4.0 minutes/100 MU to 2.0 minutes/100 MU. Increasing the delivery dose rate has also been suggested for reducing gated treatment times. Preliminary results from Linthout et al\(^15\) showed that increasing dose rate from 480 to 800 MU/min decreased treatment delivery time from 0.9 min/100 MU to 0.4 min/100 MU. Likewise, Willoughby et al\(^16\) found that increasing dose rate from 480 to 800 MU/min reduced gated treatment times by 40% when using 20% and 40% gating windows while maintaining an output consistency within 0.5%.

In this study, we investigated the dosimetric and temporal effects of RGRT by evaluating the dosimetric impacts of 4 gating windows and developing a novel algorithm for estimating the corresponding treatment delivery times when using dose rates of 500 and 1500 MU/\(\text{min}\).

**Methods**

Following institutional review board approval (#200905703), 5 patients with lung cancer treated at our institution were included in this retrospective study. All of the patients had undergone 4DCT scans. A summary of patient characteristics is listed in Table 1. Among the patients, maximum tumor motion varied from 6 to 12 mm. Two patients were treated with respiratory gating using an 80EX-80IN gating window (Table 2), while 3 patients were treated without respiratory gating. Of the patients, 1 was treated with IMRT, while the remaining 4 were treated using stereotactic body radiation therapy (SBRT). Table 3 summarizes the planning methods and prescriptions for the SBRT patients. The prescription dose varied from 8 to 18 Gy/fraction with treatment fractions varied from 3 to 5 fractions. Both static beams and IMRT were used in the SBRT planning.

**Image Acquisition**

Patient computed tomography (CT) images were acquired using the Siemens Biograph positron emission tomography CT scanner (Siemens Medical System, Knoxville, Tennessee). For each patient, a breath-hold CT scan at the end of exhale was first taken, followed by a free-breathing 4DCT scan, during which the patient’s respiratory motion was recorded using a commercially available strain gauge pressure sensing system (Anzai medical Co Ltd, Tokyo, Japan) fixed to the upper abdominal region using an elastic belt. Retrospective sorting of the 4DCT projections was performed using the CT console. Amplitude-based binning was used for image reconstruction. Each reconstructed CT image corresponded to one of 10 respiratory amplitudes: 0EX, 20EX, 40EX, 60EX, 80EX, 100IN, 80IN, 60IN, 40IN, and 20IN. The name of each respiratory phase identifies the percentage of full inhalation reached, as well as whether the phase occurs during inhalation or exhalation (eg, the 20IN phase occurs when the patient is inhaling and reaches 20% of full inhalation). A sample respiratory cycle is depicted in Figure 1.
Table 2. Gating Windows.

| Gating Window | Included Phases            |
|---------------|---------------------------|
| 20EX-20IN     | 20EX, 0EX, 20IN           |
| 40EX-40IN     | 40EX, 20EX, 0EX, 20IN, 40IN|
| 60EX-60IN     | 60EX, 40EX, 20EX, 0EX, 20IN, 40IN, 60IN |
| 80EX-80IN     | 80EX, 60EX, 40EX, 20EX, 0EX, 20IN, 40IN, 60IN, 80IN |

Table 3. Summary of Planning Methods and Prescriptions for SBRT Patients.

| Patient | Prescription | Static Beam/IMRT | Couch Angles | # of Beams |
|---------|--------------|------------------|--------------|------------|
| P1      | 10 Gy × 5    | Static           | 0°           | 6          |
| P6      | 10 Gy × 4    | IMRT             | 0°           | 11         |
| P7      | 18 Gy × 3    | Static           | 0°, 15°, 345°| 16         |
| P9      | 8 Gy × 5     | Static           | 0°, 15°, 345°| 16         |

Abbreviations: IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Deriving Target Volumes

For each patient, the breath-hold CT scan was used to generate the gross tumor volume (GTV). Contouring was performed using the Pinnacle3 treatment planning system (TPS; Philips Radiation Oncology Systems, Milpitas, California). This GTV was automatically copied to each 4DCT data set using Velocity AI deformable image registration software (Velocity Medical Systems, Atlanta, Georgia). The GTVs for each phase CT were verified to ensure conformity with the corresponding 4DCT image. Four internal target volumes (ITVs), corresponding to 4 gating windows (Table 2), were then created by performing a union of the GTVs for the phases included within the gating window.

Planning target volumes (PTVs) were derived from ITVs by adding 5 mm margins, accounting for uncertainty in patient setup. This resulted in 4 gated treatment plans (20EX-20IN, 40EX-40IN, 60EX-60IN, and 80EX-80IN) for each patient, generated to satisfy the same planning criteria as the original patient treatment plan.

Dosimetric Evaluation

Mean tumor dose (MTD), mean lung dose (MLD), and lung V20 (percentage of the lung volume receiving at least a 20 Gy dose) were used for dosimetric evaluation. The Pinnacle3 TPS was used to generate and analyze the dose–volume histogram. Percentage and absolute dose differences were computed between each gated treatment and the original treatment plan.

Calculation of Treatment Time

A MATLAB (MathWorks, Natick, Massachusetts) algorithm was developed to compute the treatment time for each plan, including time for gantry rotation, time for collimator leaves and jaws motion, time to deliver dose, and time for communication overhead. For gated treatment plans, dose delivery time was scaled relative to the time spent within the gating window based on the patient’s respiratory trace. The treatment time calculation algorithm was validated using the actual patient treatment time. Treatment times were first compared using dose rates of 500 MU/min for both gated and nongated treatment plans and then compared again using an increased dose rate of 1500 MU/min for gated plans.

Treatment time calculation. The MATLAB algorithm computed treatment delivery time by utilizing the treatment plan exported from the Pinnacle3 TPS (see Figure 2). Equation 1 describes the calculation for total treatment time ($t_{\text{total}}$), where $beam$ is the total number of beams, $t_{\text{overhead}}$ is the time of communication overhead, $t_{\text{gantry}}$ is the gantry rotation time, $CP$ is the total number of control points, $t_{\text{mech}}$ is the mechanical time for the collimator leaves and jaws, and $t_{\text{dose}}$ is the time to deliver dose.

$$t_{\text{total}} = \sum_{k=1}^{beam} (t_{\text{overhead}} + t_{\text{gantry}}) + \sum_{i=1}^{CP} (t_{\text{mech}} + t_{\text{dose}}). \quad (1)$$

Time of communication overhead ($t_{\text{overhead}}$), accounting for machine communication time, was 3 seconds for each beam based on observation. Gantry rotation time ($t_{\text{gantry}}$), as seen in Equation 2, was computed by calculating the time to travel between the current gantry angle ($\theta_i$) and previous ($\theta_{i-1}$) gantry angle, and the gantry rotation speed ($s_{\text{gantry}}$) was set to 3°/sec based on observation of the gantry rotation.

$$t_{\text{gantry}} = \frac{\theta_i - \theta_{i-1}}{s_{\text{gantry}}} \quad . \quad (2)$$

Mechanical time ($t_{\text{mech}}$), calculated Equation 3, accounts for the time to move the jaws and collimator leaves at each control point. First, an optimal sequence for the control points, which provided the shortest time, was determined by finding the sequence requiring the least movement between control points.
Next, for each control point, the distance moved by each leaf (\(y\)) and jaw (\(j\)), based on current (\(i\)) and previous (\(i - 1\)) position, was computed and divided by constants \(s_{\text{leaf}}\) and \(s_{\text{jaw}}\) for the leaves and jaws, respectively. For each control point, the maximum amount of time taken to move all leaves and jaws was defined as the mechanical time. In order to determine \(s_{\text{leaf}}\) and \(s_{\text{jaw}}\), the treatment time algorithm calculated the treatment time for each patient using varying leaf and jaw speed combinations ranging from 0.1 up to 4.0 cm/s and compared to the actual treatment time obtained from the treatment record. Based on our calculation, \(s_{\text{leaf}}\) and \(s_{\text{jaw}}\) were set to 2.0 and 1.0 cm/s accordingly.

\[
t_{\text{mech}} = \text{Max} \left\{ \left( \frac{y_i - y_{i-1}}{s_{\text{leaf}}} \right) \forall \{y\}, \left( \frac{j_i - j_{i-1}}{s_{\text{jaw}}} \right) \forall \{j\} \right\}. \tag{3}
\]

As shown in Equation 4, time to deliver dose (\(t_{\text{dose}}\)) was also calculated for each control point of the beam. Number of monitor units for each control point (\(MU_{\text{CP}}\)) was first calculated by multiplying the total prescribed monitor units (\(MU_{\text{total}}\)) by the beam weighting (\(w_{\text{beam}}\)) and the control point weighting (\(w_{\text{CP}}\)). Time to deliver dose was then calculated by dividing \(MU_{\text{CP}}\) by the dose rate (DR) and gating factor (GF). Gating factor was derived from the patient’s respiratory trace and defined as the fraction of the respiratory signal contained within the gating window (\(\text{Resp}_{\text{GW}}\)) versus the total respiratory signal (\(\text{Resp}_{\text{total}}\)).

\[
t_{\text{dose}} = \frac{MU_{\text{CP}}}{DR \times GF},
\]

where \(MU_{\text{CP}} = MU_{\text{total}} \times w_{\text{beam}} \times w_{\text{CP}}\) and \(GF = \frac{\text{Resp}_{\text{GW}}}{\text{Resp}_{\text{total}}}\). \tag{4}

Validation of treatment time algorithm. To validate the treatment time algorithm, actual treatment times for 5 enrolled patients were obtained from the MOSAIQ treatment record and verify system (Elekta, Stockholm, Sweden) and compared against computed treatment time. Because patients received multiple fractions, treatment time for each fraction could vary depending on the consistency of breathing, and whether the machine encountered problems during delivery, the actual treatment time was defined as the average treatment time across all fractions. Any obvious outliers were excluded during calculation of the average treatment time.

Results

Results were divided into 2 groups: (1) patients whose original treatment plan was nongated and (2) patients whose original treatment plan was gated using an 80EX-80IN gating window (refer to Table 2). In the first group, the evaluated 20EX-20IN...
to 80EX-80IN treatment plans were compared against the original nongated plan. In the second group, the evaluated 20EX-20IN to 60EX-60IN treatment plans were compared against the original 80EX-80IN gated plan.

**Dosimetric Evaluation for Nongated Patients**

The average reduction in PTV volume was $-26.9\% \pm 4.4\%$, $-21.8\% \pm 4.2\%$, $-15.4\% \pm 2.6\%$, and $-9.4\% \pm 6.0\%$, respectively, for the 20EX-20IN, 40EX-40IN, 60EX-60IN, and 80EX-80IN gated plans when compared to the nongated plan (Figure 3). The PTV coverage for all gated plans was kept within $1\%$ of the original PTV coverage, and the MTD was kept within $<1\text{ Gy}$ of the original MTD. The percentage of difference in MTD was $<2\%$ across plans for all patients (Figure 4). Figures 5 and 6 show the relative percentage of differences in MLD and lung V20 across plans for each patient. Both MLD and lung V20 were found to decrease as we reduced the gating window. On average, relative percentage differences in MLD and lung V20 were reduced by $-16.1\% \pm 1.0\%$ and $-20.0\% \pm 2.3\%$ for 20EX-20IN-gated plans, $-12.5\% \pm 1.0\%$ and $-15.6\% \pm 2.3\%$ for 40EX-40IN-gated plans, $-8.7\% \pm 3.5\%$ and $-11.1\% \pm 4.2\%$ for 60EX-60IN-gated plans, and $-6.0\% \pm 4.7\%$ and $-7.2\% \pm 5.7\%$ for 80EX-80IN-gated plans when compared to the nongated plan.

**Dosimetric Evaluation for 80EX-80IN-Gated Patients**

For patients originally gated at 80EX-80IN, the average reduction in PTV volume was $-29.1\% \pm 7.7\%$ for the 20EX-20IN-gated plans, $-26.9\% \pm 7.8\%$ for the 40EX-40IN-gated plans, and $-21.3\% \pm 5.2\%$ for the 60EX-60IN-gated plans when compared to the 80EX-80IN-gated plan (Figure 3). The PTV coverage for all gated plans was kept within $1\%$ of the original PTV coverage, and the MTD was kept within $<1\text{ Gy}$ of the original MTD. The percentage of difference in MTD was $<1\%$ across plans for all patients (Figure 4). Figures 5 and 6 show the relative percentage of differences in MLD and lung V20 across plans for each patient. Both MLD and lung V20 were on average found to be reduced $-5.8\% \pm 1.4\%$ and $-7.0\% \pm 4.3\%$ for the 20EX-20IN-gated plans, $-4.7\% \pm 0.0\%$ and $-6.0\% \pm 2.9\%$ for the 40EX-40IN-gated plans, $4.2\% \pm 0.3\%$ and $-5.4\% \pm 2.1\%$ for the 60EX-60IN-gated plans.

**Validation of Treatment Time Algorithm**

Table 4 compares the results of the treatment time calculation algorithm with the actual treatment time obtained from the treatment records. On average, the algorithm was able to estimate treatment time within $-0.8\text{ minutes} (-7.0\%)$ of the actual
In 4 of 5 patients, the algorithm was able to predict treatment time within <1 minute of the actual time.

**Treatment Time Comparison for Nongated Patients**

The left-hand side of Figure 7 depicts the percentage difference in treatment times between the nongated plans and their corresponding 20EX-20IN- to 80EX-80IN-gated plans. When using a dose rate of 500 MU/min for both the nongated and gated plans, treatment delivery times were on average found to increase by 16.9% ± 23.4% (0.08 ± 0.10 min/100 MU), 4.9% ± 12.8% (−0.01 ± 0.10 min/100 MU), and 4.6% ± 0.9% (0.04 ± 0.03 min/100 MU), respectively. Patient 8 did not exhibit the same pattern in treatment time as seen in the remaining patients (smaller gating windows required more time) but rather had relatively similar treatment times across the 4 gated plans.

Treatment times were next compared using an increased dose rate of 1500 MU/min for the 20EX-20IN- to 60EX-60IN-gated plans while keeping the original 80EX-80IN-gated plan at 500 MU/min. Figure 8 outlines these results. By increasing the dose rate for the gated plans, treatment times were on average found to be reduced by −15.6% ± 5.2% (−0.15% ± 0.09 min/100 MU), −20.3% ± 7.9% (−0.19 ± 0.11 min/100 MU), and −17.7% ± 15.5% (−0.12 ± 0.01 min/100 MU), respectively. In the case of patient 8, the 60EX-60IN-gated plan took longer to deliver than the 20EX-20IN- and 40EX-40IN-gated plans.

**Discussion**

As has been demonstrated in previous RGRT studies,8,9,11,12 the PTV for all patients could be reduced, indicating a smaller total volume received the target dose. The PTV coverage and MTD were able to be maintained, suggesting that the target was just as effectively able to be treated. Furthermore, MLD and lung V20 were shown to decrease when smaller gating windows were selected. For the smallest gating window, 20EX-20IN, MLD was on average reduced by −16.1% ± 1.0% in originally nongated plans and by −5.8% ± 1.4% in plans originally gated 80EX-80IN, an absolute difference of
Dose rate. As can be seen in Figure 8, raising the dose rate for gated treatment plans may be reduced by increasing the increase time by 4.9\%\textsuperscript{80EX-80IN gating window was on average only found to an absolute difference of 0.13\%\textsuperscript{80EX-80IN gating window was on average only found to an absolute difference of 0.13\}. Some authors\textsuperscript{11,13} have pointed out that the direct links between the originally gated 80EX-80IN and an absolute difference of 0.07 min/100 MU, while the 80EX-80IN gating window included 9 respiratory phases (20EX, 0EX, and 20IN), while the 20EX-20IN gating window included 3 respiratory phases (20EX, 0EX, and 20IN). Some authors\textsuperscript{11,13} have pointed out that the direct links between the dosimetric benefits of respiratory gating and successful patient outcome are unknown. However, MLD and lung V20 have been used clinically as predictive factors for radiation pneumonitis.\textsuperscript{17,18} Although no studies have directly evaluated the effects of respiratory gating on radiation pneumonitis, results of these dosimetric studies imply that respiratory gating may reduce the risk of radiation pneumonitis. When selecting patients for respiratory gating and choosing appropriate gating windows, the dosimetric benefits of gated treatment should be weighed along with the clinical risk for radiation pneumonitis.

As shown in Figures 7 and 8, smaller gating windows required longer delivery times when dose rate was unchanged. This was expected due to the fact that dose delivery for gated treatment is intermittent rather than continuous. However, time increase was not found to be linearly proportional to the number of respiratory phases within the gating window. This is likely because patients spent more time in the exhalation phase of respiration. For example, the 20EX-20IN gating window includes 3 respiratory phases (20EX, 0EX, and 20IN), while the 80EX-80IN gating window includes 9 respiratory phases (80EX, 60EX, 40EX, 20EX, 0EX, 20IN, 40IN, 60IN, and 80IN), although, as we see Figure 9, patients did not spend 3 times longer in the 80EX-80IN window as they did in the 20EX-20IN window. Patients 8 did not exhibit the same patterns in treatment time as seen in the remaining patients (smaller gating windows required more time) and instead had relatively similar treatment times across the 4 gated plans. This is likely due to the patient spending a majority of the breathing cycle in the full exhalation phase (0EX) of respiration, thereby giving similar gating factor for the 20EX-20IN (60\%), 40EX-40IN (70\%), 60EX-60IN (78\%), and 80EX-80IN (89\%) gating windows. Further investigation also indicates that for this patient, the mechanical time took longer for the 60EX-60IN (87 seconds) and 80EX-80IN (82 seconds) gating windows than for the 20EX-20IN (69 seconds) and 40EX-40IN (63 seconds) gating windows. The combination of similar gating factor and shorter mechanical times for the smaller gating windows allowed for comparable treatment times across the 20EX-20IN- to 80EX-80IN-gated plans.

Treatment delivery time is an important consideration when selecting an optimal treatment plan. Prolonged treatment delivery times can affect patient comfort and compliance. Advances in radiotherapy delivery techniques, such as VMAT, have led to the potential for reduction in treatment delivery times. Arc therapy allows for continuous delivery of radiation, thereby increasing the delivery efficiency. In contrast, techniques such as “step-and-shoot” IMRT require increased time for therapy because delivery is not continuous. Particularly for cases that require longer treatment delivery times, having the ability to estimate delivery time through this algorithm may aid in selecting patients for respiratory gating and choosing appropriate gating windows. When presented with 2 treatment plans with similar dose distributions, treatment time information may be useful in selecting the optimal plan. Additionally, the temporal effects of factors such as dose rate may also be assessed and used to aid in planning. The biggest limitation to this study was the small patient sample size (n = 5), which was made smaller by separating patients who had been treated using 80EX-80IN-gated treatment (n = 2) from those who had undergone nongated treatment (n = 3). The next step in this research will be to repeat this study using a larger patient sample size and perform a statistical analysis. An increased sample size will allow us to further validate the treatment time calculation algorithm as well as determine factors that have the largest impact on delivery time. Additionally, we will be able to investigate which parameters, such as maximum tumor motion or size of GTV, are most useful in predicting the potential benefits of respiratory gating.

**Conclusion**

Respiratory-gated radiation therapy in patients with lung cancer can reduce lung dose while maintaining tumor dose. Because treatment delivery during gated therapy is discontinuous, total treatment time may be prolonged. However, this increase in treatment time can be offset by increasing the dose delivery rate. Estimation of treatment time may be helpful in
selecting patients for respiratory gating and choosing appropriate gating windows.

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