The evaluation for the hemodynamics of pelvic arteries in double balloon occluded arterial infusion therapy (BOAI) in comparison with single BOAI in patients with bladder cancer using syngo iFlow

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Aims and objectives

The gold standard of therapy for locally invasive bladder cancer has long been radical cystectomy with pelvic lymph node dissection. However, about 50% of all patients with invasive bladder cancer die, and its outcome is closely related to pathologic stage [1].

A highly effective, but honor minimally invasive therapy that conserves the bladder is therefore needed. Combined treatment involving radical transurethral resection, chemotherapy, and radiation therapy has been attempted as an alternative approach for patients who require cystectomy.

The novel bladder preservation therapy, known as OMC-Regimen, using double balloon occluded arterial infusion (BOAI) has resulted in a good clinical response [2]. Compared with conventional single balloon occluded catheter (S-BOC), double balloon occluded catheter (D-BOC) method allows the accumulation of anticancer agent at a high concentration at the site of a tumor without flowing of anticancer agent to other tissues.

So far we`ve visually confirmed more accumulation of contrast enhanced medium (CEM) to the tumor site at the angiography using D-BOC than S-BOC, which might be related to the good clinical response. But there hasn`t been any clinical research evaluating the hemodynamics on BOAI procedure for the patients with bladder cancer objectively. Recently syngo iFlow (Siemens Healthcare) which provides objective and quantitative angiographic information has enabled to analyze the difference in hemodynamic status of the pelvic vessels between using D-BOC and S-BOC. Therefore this study aims to elucidate the quantitative difference in hemodynamics of the bladder arteries in patients with bladder cancer between using D-BOC and S-BOC.
Methods and materials

Patients

Our institutional review board approved this retrospective study; prior written informed consent was obtained from all patients for Balloon Occluded Arterial Infusion (BOAI). Between November 2013 and May 2014, we performed clinically indicated BOAI for the patients with bladder cancer. Eligible patients had histologically confirmed carcinoma in situ (CIS) or stage T2, T3 or T4 muscle-invasive bladder cancer without distant metastasis. Imaging studies, including chest and abdominal computed tomography (CT) scan, abdominal/pelvic magnetic resonance imaging (MRI) and bone scintigraphy were performed before the start of therapy. From the digital subtraction angiography (DSA) series collected for the 57 patients, 30 patients (23 men, 7 women; mean age 64.4 years, range 46-83 years) were successfully postprocessed by using Quantitative Digitally Subtracted Angiography (syngo iFlow; Siemens AG, Medical Solutions, Healthcare Sector, Forchheim, Germany). 27 patients were excluded because the catheter could not be placed in the right position due to severely tortuous arteries.

BOAI Procedure and Imaging Protocol

For the intra-arterial infusion procedure, we used an intra-arterial catheter equipped with 2 occlusion balloons (size: 6 Fr., M6F-28-70-TBSB4-ST, Clinical Supply, Tokyo, Japan). The catheter was introduced into the posterior trunk of internal iliac artery via contralateral femoral artery access, and after the distal balloon had passed through the furcation of the anterior trunk of the internal iliac artery, both the distal and proximal balloons were inflated and immobilized, so that the anterior trunk of the internal iliac artery, which lies upstream of the target vessels, the "bladder arteries," was isolated between the balloons (Fig.1). At this time, using DSA, it was confirmed that the injected agent did not enter the superior gluteal artery and that there was no back-flow into the internal iliac artery, whereas the tumor was markedly stained because of active flow of injected contrast medium into the urinary bladder. In the process of intra-arterial infusion chemotherapy as part of OMC regimen, various amounts of cisplatin (100, 200, or 300mg) were locally infused through both side holes between the distal and proximal balloons over a 1-hour period. In this study the DSA images of double balloon occluded catheter (D-BOC) and single balloon occluded catheter (S-BOC) in which only proximal balloon was inflated were acquired. Figure 2 represents the DSA images of D-BOC (A) and S-BOC (B).

All angiograms were obtained by using the same angiography equipment and injection parameters after bilateral catheters were connected to one high-pressure-resistant extension tube from a contrast media injector (Mark V ProVis®. Angiographic Injection
System; MEDRAD). DSA was performed with the following parameters: 10 mL iopamidol (370 mgI/mL) injected at a rate of 1.5 mL/s, anteroposterior position, rate of 4 frames per second. The DSA series were then postprocessed by using syngo iFlow for analysis.

**Postprocessing of DSA Images**

Both D-BOC and S-BOC DSA data (Fig.2) were transferred to a dedicated image reconstruction workstation (syngo X-Workplace; Siemens). Then the hemodynamic parameters were assessed with syngo iFlow software. syngo iFlow provides a single image that shows the history of the contrast media through the vessels in color (color-coded single image) by calculating and displaying time density curves (TDCs) for each image pixel (Fig.3). The time to peak enhancement (TTP) and area under curve (AUC) were identified from each of these pixel-specific curves. TTP is represented by a color (ranging from red to blue) representing early, middle and late flow in a series of the DSA. It enables to evaluate the inflow and outflow of contrast in dedicated pixels or in regions of interest (ROIs). Hemodynamic parameters of AUC in the ROI represent the total amount of contrast agents that run inside ROI in a series of DSA. The color-coded image makes it easy to assess contrast flow within arteries by showing a complete DSA run in a single image.

**Data and Statistical Analysis**

On the color-coded single image of S-BOC, ROIs were placed on both side holes of the catheters, superior gluteal arteries (SGAs), inferior gluteal arteries (IGA) and bladder arteries (BAs) (Fig 4). Each ROI placed on the color-coded image of S-BOC was automatically transferred to the same position on the color-coded image of D-BOC. The ROI on the side hole of the catheter was defined as reference point (Ref-P) when using syngo iFlow. Since bilateral catheters were connected to one tube from a contrast media injector, each amount of contrast media through the side hole was regarded as equal. Then TDCs of the other ROIs were analyzed. The AUC was calculated as the sum of the relative density to that of Ref-P at each time point divided by the frame rate. Total relative perfusion was estimated by the calculated AUC from the initial first pass perfusion to 25 sec. Those calculated AUC parameter is not absolute value but the comparative parameter that is calculated as the AUC of the ROI divided by AUC of Ref-P (Fig3). Therefore comparative value (CV) for each ROI is calculated as follow:

CV = AUC of the ROI / AUC of the ipsilateral Ref-P

Then we evaluated the change in CVs for SGA, IGA and BA between D-BOC and S-BOC. The change in CV was defined as the ratio of the CV for the ROI using D-BOC to that using S-BOC to confirm how much larger the amount of contrast media ran through
in the ROI using D-BOC compared to S-BOC. So the calculation in assessment of the change is as follow:

The change in CV = CV for the ROI using D-BOC / CV for the ROI using S-BOC
Fig. 1: The scheme of double BOAI (a) and single BOAI (b) 6Fr double balloon catheters is introduced into the both superior gluteal arteries via contralateral femoral artery access. Both side holes between the distal and proximal balloons are placed at the origins of each bladder arteries so that the active flow of injected agent into the urinary bladder is established.

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Fig. 2: The two patterns of BOAI angiography for a 52-year old man with invasive urothelial carcinoma. (a) The angiography with both distal and proximal balloons inflated (D-BOC) (b) The angiography with only proximal balloon inflated (S-BOC) The more accumulation of contrast enhanced medium to the bladder arteries in D-BOC is visually confirmed than in S-BOC (arrows).

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Fig. 3: The color-coded images after post-processing DSA images of the same patient as in figure 2 using syngo iFlow. (a) The angiography with both distal and proximal balloons inflated (D-BOC) (b) The angiography with only proximal balloon inflated (S-BOC) The ratio of the amount of blood flow into bladder arteries using D-BOC is much more than those using S-BOC. (Right: 1.44-fold, Left 1.92-fold)

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Fig. 4: The color-coded images and time density curves (TDCs) after injection of contrast enhanced medium. (a) The angiography with both distal and proximal balloons inflated (D-BOC) (b) The angiography with only proximal balloon inflated (S-BOC) Red, pink, blue and green regions of interests (ROIs) were placed on the ipsilateral side hole of the catheter, bladder artery, inferior gluteal artery, superior gluteal artery, respectively. The red ROI (on the side hole of the catheter) was defined as reference point (Ref-P). The AUC (area under the curve) was calculated as the sum of the relative density to that of Ref-P at each time point divided by the frame rate.

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Results

The result was shown on Table 1. The average changes in CV for BA and IGA were 3.04-fold (median 1.86, range 0.62-46) (Right: 3.59-fold, Left: 2.51-fold) and 1.77-fold (median 1.39, range 0.20-11.6) (Right: 1.80-fold, Left: 1.73-fold) respectively. Whereas the average change in CV for SGA was 0.44-fold (median 0.32, range 0.09-1.62) (Right: 0.44-fold, Left 0.42-fold).
Table 1: The changes in CV (CV for the ROI using D-BOC / CV for the ROI using S-BOC) for BA, IGA, and SGA CV(comparative value)= AUC of the ROI/ AUC of the ipsilateral Ref-P BA=bladder artery, IGA=inferior gluteal artery, SGA=superior gluteal artery, D-BOC=double balloon occluded catheter, S-BOC=single balloon occluded catheter

<table>
<thead>
<tr>
<th>The change in CV</th>
<th>Average(Right) (fold)</th>
<th>Average(Left) (fold)</th>
<th>Median (fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>3.59</td>
<td>2.51</td>
<td>1.86(range 0.62-46)</td>
</tr>
<tr>
<td>IGA</td>
<td>1.80</td>
<td>1.73</td>
<td>1.39(range 0.20-11.6)</td>
</tr>
<tr>
<td>SGA</td>
<td>0.44</td>
<td>0.42</td>
<td>0.32(range 0.09-1.62)</td>
</tr>
</tbody>
</table>
Conclusion

In comparison with subjective and qualitative evaluations in the accumulation of CEM during DSA procedure, syngo iFlow provides a method to extract physiologic information from standard DSA series. The software tool displays dynamic information in a colorful static image, in which different-colored scales mark the history of the contrast media through vessels. Therefore, quantitative measurements of the hemodynamic condition are recorded and depicted by using syngo iFlow. There are some reports for analysis of hemodynamics using syngo iFlow in the fields of head and neck or liver [3-5].

In our hospital, newly developed bladder preservation therapy for the patients with invasive bladder cancer using double BOAI of an anticancer agent known as OMC regimen has been performed for 20 years, and has left better treatment outcome than conventional treatment of radical cystectomy with pelvic lymphnode dissection [1]. Although double BOAI method has been assumed to deliver an extremely high concentration of anticancer agent to the site of a tumor since more accumulation of CEM to the tumor site has been confirmed visually at the angiography using D-BOC than S-BOC, the assessment of quantitative alterations in pelvic vessel hemodynamics due to the introduction of double balloon-occlusion in comparison with single balloon-occlusion by using syngo iFlow has never been reported. The use of syngo iFlow provides several advantages. First, the application of syngo iFlow does not require additional x-ray dosages. Standard DSA acquisitions are used to generate color-coded images and obtain quantitative information. Second, iFlow is a real-time tool. Color-coded images with quantitative measurements are obtained immediately after the DSA series is acquired. Third, hemodynamic conditions and changes can be quantitatively analyzed with parameters such as TDC through syngo iFlow. iFlow focuses not only on alterations in the flow dynamics of the tumor feeding vessel, but also on tumor perfusion, which is represented by the area under the TDC.

In this study, the more accumulation of CEM to the bladder arteries and the less accumulation of CEM to the superior gluteal arteries using D-BOC were quantitatively proved than using S-BOC. We assume that the alteration in the accumulation of CEM to the bladder arteries by using D-BOC lead to the increase of anti-cancer drug concentration to the bladder in OMC-regimen, resulting in better clinical response.

The present study has several limitations. First, the difference in the clinical response to the treatment between using S-BOC and D-BOC could not be evaluated since all patients in this study were treated by using D-BOC. Second, all parameters assessed by iFlow are not absolute values but the comparative ones. Therefore setting the ROI on Ref-P should be needed to calculate the TDC of one particular ROI. In this study the TDC of Ref-P
using D-BOC was regarded as same as that using S-BOC because Ref-P was put on the side hole of the same catheter. However, as seen in Fig.4, the shape of TDC of Ref-P using D-BOC was different from that using S-BOC especially just after the end of the contrast medium injection. One potential reason is that the occlusion of SGA may cause backward flow of IGA to compensate for the lack of the blood supply to SGA, leading to the change in blood perfusion of the Ref-P as well as IGA and BA. Furthermore the change in the TDC of Ref-P affects the shape of the other TDCs.

In conclusion using D-BOC increased the amount of CEM into bladder arteries twice as much as using S-BOC quantitatively. This may result in higher concentration of anticancer drug in the affected bladder, leading to a good clinical response.
References


