How to avoid hemorrhage-related confounding in Prostate MRI

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Purpose

In Taiwan, the incidence and the mortality rate of prostate cancer is increasing yearly.[5]. Moreover, the prostate cancer becomes the one of the leading causes of cancer death in men. According to the "Clinical practice guideline for the diagnosis and treatment of prostate cancer" written by Taiwan cooperative oncology group[4], ultrasonographically guided transrectal biopsy is recommender when PSA level is elevated (cutoff level: 3.5-4.0ng/ml)or positive finding of digital examination. To confirm the diagnosis of the prostate cancer is based on histological findings of biopsy. After the tissue proof, some patients may receive MRI study before the operation. In MRI study, we not only define the zonal anatomy of prostate gland but also figure out the tumor size and tumor extension. The finding of extracapsular extension is crucial for tumor staging, prognosis, and clinical management.

The zonal anatomy of prostate gland is best recognized on T2-weighted image. Although the transitional zone consists only 5% in young man, benign prostate gland hypertrophy which is a common disease in elder man enlarges the transitional zone markedly. Moreover, the signal intensity of the central zone and transitional zone are similar and we cannot figure out the junction between them on MR images. In this study, the term of "central zone" covers the central zone and the transitional zone histologically. For delineating the peripheral zone and central zone, there is linear boundary between the peripheral zone and central zone, called prostate pseudocapsule or surgical capsule (Figure 1B.). [3] In addition, due to the different inherent signal intensity, the peripheral zone shows relative higher signal intensity than the central zone on T2-weighted image (figure 1B.). There is a thin hypointense rim surrounding to peripheral zone as anatomic or true capsule. The closer the tumor related to the true capsule; the possibility of extracapsular extension to seminal vesicles and neurovascular bundles is higher.

We identified the prostate cancer by depicting an area of low signal intensity on T2-weighted image. However, when presenting with post-biopsy hemorrhage, the diagnosis becomes challenging because the signal from hemorrhage may obscure the tumor and result in over-diagnosis or under-estimate (Figure 1). The overcome this situation, some authors suggest prolong the period between the transrectal biopsy and MRI to 3 weeks in order to avoid hemorrhage-related confounding.[6; 16] In this study, we surveyed the possible parameters which may contribute to post-biopsy hemorrhage in order to determine which one of them should be surveyed routinely before biopsy.
**Fig. 0:** The zonal anatomy of the prostate gland and post-biopsy hemorrhage. A. T1-weighted axial image shows a high signal intensity in the left peripheral zone. B. T2-weighted axial image. The peripheral zone (PZ) shows higher signal intensity than the central zone (CZ). There is a thin hypointense junction between the peripheral zone and central zone as pseudocapsule (black arrowhead). Another thin hypointense rim surrounding the peripheral zone is the true capsule (black arrow). There are two hypointense lesions in the left central zone and the peripheral zone. The red line outlines the hemorrhage as compared with T1-weighted axial image. The blue lines outline the cancerous foci as compared with the whole-mount specimen (Figure 1C. and 1D.). Notice that the range of the hemorrhage covers the cancerous foci in the peripheral zone resulting under-interpretation. C.&D. The whole mount specimen from radical prostatectomy. The blue lines outlining the cancerous foci are drawn by the pathologist.
Methods and Materials

We retrospectively surveyed patients who received prostate MRI during January 2003 to December 2010 in a single institution. The inclusion criteria include (1) patients received ultrasonographically guided transrectal biopsy and followed by prostate MRI (2) the period between the biopsy and MRI is less than 180 days. For those patients who could not trace the definite time of biopsy and/or definite pathologic report, received hormonal or radiation therapy before the MRI study were all excluded. Total 234 patients enrolled in this study (mean age 67, range 30-87). The systemic biopsy was carried out by several experienced urologists with 18-gauge needle. From upper, middle to lower directions, total 12 sectors (right peripheral, right parasagittal, left peripheral and left parasagittal) were biopsied (Figure 1).

MRI imaging

For the patients who received MRI before March 2010, the MRI images were performed on a 1.5T scanner (Magnetom Avanto; Siemens Healthcare, Malvern, PA) with a balloon-covered expandable endorectal coil. And for those who received MRI after March 2010, the MRI images were all performed on a 3.0T scanner (Intera Achieva 3.0T, Philips Medical System, Best, the Netherlands) without endorectal coil. All patients were examined using the body coil for excitation and pelvic phased-array coil for signal reception. The protocol include transverse, coronal, and sagittal T2-weighted fast spin-echo imaging, transverse nonenhanced and contrast-enhanced T1-weighted fast spin-echo imaging, transverse DW imaging (b=0 and 800 sec/mm^2), transverse apparent diffusion coefficient and transverse dynamic contrast-enhanced imaging. We used the plane connecting from base to apex of prostate gland in mid-sagittal view as the direction of coronal cut and its perpendicular plane as the direction of axial view (Figure 2).

Image interpretation and data analysis

A more than 10-year-experienced radiologist reviewed all the images and recorded the presence of prostate cancer and hemorrhage areas. The reviewer was unaware of the histological finding and clinical status. The definition of hemorrhage on MRI is the presence of high signal intensity areas in T1-weighted image. The locations of the hemorrhage including peripheral zone, central zone, seminal vesicles, bilateral locations, "left side only" and "right side only" were recorded respectively. The diagnosis of prostate cancer is making by comparing different pulse sequences carefully to avoid mis-interpretation.

We retrospectively collected the laboratory data including platelet count, partial thromboplastin time (PT), activated partial thromboplastin time (aPTT), prostate-specific
antigen (PSA) and pathological results of Gleason's score, past history of diabetes mellitus, and past history of hypertension. Only those laboratory data within 3 months before or after the transrectal biopsy would be restrictively taken accounted in this study. All the patients were divided into two groups: Non-hemorrhage and hemorrhage. We compared the discrimination of period, recorded laboratory data and past history between these two groups.

We used Microsoft excel 2007 (Microsoft®) for statistical analysis. T-test was used for continuous parameters and Chi square for non-continuous parameters. All statistical tests were counted on two tail condition and a $p$-value <0.05 was considered to be statistically significant.
Images for this section:

**Fig. 0:** The 12 sectors of systemic 12-core-transrectal biopsy. From upper, middle to lower directions, total 12 sectors (right peripheral, right parasagittal, left peripheral and left parasagittal) were included. A. Axial view, from right to left: a. Right peripheral b. Right parasagittal c. Left parasagittal d. Left peripheral (CZ=central zone, PZ=peripheral zone, R=rectum.) B. Sagittal view, from top of image to bottom: U. Upper M. Middle L. Lower (UB=urinary bladder, R=rectum.)

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**Fig. 0:** The directions of coronal and axial image. T2-weighted mid-sagittal image. The plane connecting from base to apex of prostate gland in mid-sagittal view as the direction of coronal cut (white line) and its perpendicular plane as the direction of axial view (dotted line). (UB=urinary bladder, P=prostate gland, R=rectum, S=sacrum.)

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Results

RESULTS

In total 234 patients, there were 181 patients observed to have hemorrhage on MRI scan and were classified as the hemorrhage group. The average age is 66.7 years old in hemorrhage group and 67.1 years old in non-hemorrhage group \( (p=0.72) \). The median period between the transrectal biopsy and MRI study in non-hemorrhage group and hemorrhage group were 48 days (range 17-81) and 38 days (range 6-83). High significant difference in period \( (p=0.00165) \) is found in between these two groups (Figure 1, Table 1).

In addition, when considering the locations of the hemorrhage, hemorrhage occurred more often in the peripheral zone (56%) as compare to central zone (30.7%) and seminal vesicle (13.2%). Bilateral (50.8%) hemorrhage happened more often (Table 2) than "left side only" (30.9%) and "right side only" (18.2%).

Continuous parameters

With regard to Gleason's score, no significant correlation between the non-hemorrhage group (average 6.38, range 0-9) and the hemorrhage group (average 6.34, range 0-10) were found \( (p=0.863) \). On considering PSA level, no significant correlation between the non-hemorrhage group (average 13.89, range 3.78-52.72) and the hemorrhage group (average 19.60, range 0.05-280) either \( (p=0.246) \). Besides, there were no significant correlation between the hematologic status which is contributing to hemorrhage, including partial thromboplastin time \( (p=0.958) \), activated partial thromboplastin \( (p=0.0635) \) and platelet count \( (p=0.467) \) (Table 1).

Non-continuous parameters

Regarding diabetes mellitus and hypertension, no significant correlation between the non-hemorrhage and the hemorrhage group is also noted \( (p=0.227 \) and \( p=0.184, \) respectively) (Table 1).

Table 1 Analysis of the continuous and non-continuous parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-hemorrhage group (N=number of patient)</th>
<th>Hemorrhage group (N=number of patient)</th>
<th>( P )- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-continuous parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2 The locations of hemorrhage

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central zone</td>
<td>79</td>
<td>30.7%</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>144</td>
<td>56.0%</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>34</td>
<td>13.2%</td>
</tr>
<tr>
<td>Bilateral</td>
<td>92</td>
<td>50.8%</td>
</tr>
<tr>
<td>Left side only</td>
<td>56</td>
<td>30.9%</td>
</tr>
<tr>
<td>Right side only</td>
<td>33</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Although low signal intense areas on T2-weighted image may represent as prostate cancer, low signal intensities on T2-weighted image are observed in several different situations, such as nonspecific inflammation, post-biopsy hemorrhage, post-radiation, post-hormone therapy and dystrophic changes. [13; 14; 16] Among these conditions, post-biopsy hemorrhage is the most common one to interfere with diagnosis of prostate cancer. Currently, radiologists use several different pulse sequences to aid in diagnose of prostate cancer, including diffusion-weighted image, dynamic contrast-enhanced MR image and MR spectroscopy. However, there are still some hemorrhage-related confoundings. The susceptibility effects and the effects of intratumoral hemorrhage result in image distortion on diffusion-weighted image and apparent diffusion coefficient.[10] In addition, abnormal enhancement could be observed in hemorrhage areas on dynamic contrast-enhanced MR due to formation of granulation tissue. [11] According to Quayyum
et al, although the spectral degradation was found to unrelated to the presence of visible post-biopsy hemorrhage, it is seen predominantly in the first 8 weeks after biopsy. [12] The post-biopsy hemorrhage and the period between the transrectal biopsy and MRI study remain the role factors affecting MRI interpretation of prostate cancer.

In this study, we found that the prevalence of post-biopsy hemorrhage is quite high (77.4%). The finding is compatible with previous studies (28-77%). Furthermore, when the period is longer than 8 weeks, the estimated rate of hemorrhage will be decreased to 13%. Just as the study of Qayyum et al., we recommended an 8-week interval between the transrectal biopsy and MRI study to avoid hemorrhage instead of a 4-week interval recommended in the clinical practice guideline.

We also noted that the prevalence of hemorrhage is higher in the peripheral zone than the central zone. This result is similar to the study of Tamada et al. [15] According to some authors, the tissue in the peripheral zone consists more citrate than the central zone. This kind of citrate possesses the ability of anticoagulation and easier to cause hemorrhage. [7; 17] However, prediction of citrate level before biopsy is quite difficult.

We assesses the laboratory data used in daily practice to indicate the bleeding tendency of the patients who received transrectal biopsy, including PT, aPTT, and platelet count. But no significant correlation is noted between the non-hemorrhage group and the hemorrhage group.

As for diabetes mellitus and hypertension factors, the former one may delay the wound healing and the latter one may prolong active bleeding. Non of them had significant correlation between the non-hemorrhage and the hemorrhage groups. Under the above hints, we conclude that these two groups in this study are being statistically sampled from same population. Therefore, checking the laboratory data of bleeding tendency and reviewing past history of diabetes mellitus or hypertension still cannot predict the possibility of hemorrhage in advance.

Recently, Ahmed et al. reviewed literatures and recommended pre-biopsy MRI for the patients with high risk of prostate cancer. These patients may take advantage of increasing the detectability of prostate cancer which requires treatment while avoiding biopsy. [1] Furthermore, according to the experience of most urologists in Taiwan, prostate cancer is highly suspected when presence of positive findings of both the digital examination and high PSA level before transrectal biopsy. Pre-biopsy MRI may become another solution to overcome hemorrhage-related confounding in the future.

Limitation
There were several limitations in our study. First, the laboratory data of bleeding tendency and the past history were not available in each patient and the study was a retrospective one. Furthermore, the bleeding tendency was not evaluated routinely before the biopsy and some of the data was obtained even after the biopsy. Second, the inherent differences in image quality between 1.5T scanner and 3.0T scanner may affect the result.
**Fig. 0**: Boxplot distribution of period for non-hemorrhage group and hemorrhage group. The top and bottom of boxes indicate 25th-75th percentiles of data values. The lines in box indicate the median value.

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Conclusion

In order to avoid hemorrhage-related confounding in MRI, the period between the transrectal biopsy and MRI study is the most important factor. An 8-week interval is recommended as a safety margin for avoiding confounding factor in MRI diagnosis of prostate cancer.
References

**Personal Information**

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