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# Residual Tumor Potentially Left Behind After Local Ablation Therapy in Prostate Adenocarcinoma

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## Abstract

**Purpose—**We examined contralateral prostate cancer potentially left behind by focal therapy.

**Materials and Methods—**We investigated 100 completely embedded radical prostatectomy specimens in which needle biopsy predicted limited disease (less than 3 positive cores, 50% or less involvement of any positive core, Gleason score 6 or less) and all positive needle cores were unilateral. Clinical stage was T1c in 85 and T2a in 15 cases with the palpable lesion on the positive biopsy side.

**Results—**There was 1 positive core in 66 cases. On average 13.9% of each positive core was involved with tumor. The mean number of separate tumor nodules per radical prostatectomy was 2.9. In 65 radical prostatectomy specimens there was some tumor contralateral to the positive biopsy side. Total tumor volume in the radical prostatectomy contralateral to the positive biopsy side averaged 0.2 $cm^3$ (largest 1.3). In 23 cases contralateral tumor volume was greater than biopsy positive side tumor volume. There were 13 cases in which more than 0.5 $cm^3$ cancer was contralateral to the positive biopsy and 7 with predominantly anterior tumor. Volume contralateral to positive biopsy side could not be predicted by the number of positive cores (1 vs 2) or maximum percent of the core involved. Gleason pattern 4, extraprostatic extension or positive margins were seen contralateral to the positive biopsy side in 13, 1 and 2 cases, respectively.

**Conclusions—**In a highly selected population with limited unilateral biopsy cancer, tumor contralateral to the positive biopsy side at radical prostatectomy is typically small. However, 20% of radical prostatectomy specimens had some contralateral adverse pathology in terms of size, extraprostatic extension, grade or margins.

### Keywords

prostatic neoplasms; cryosurgery; prostatectomy

With the introduction of PSA screening test and transrectal ultrasound guided prostate biopsy, the detection rate of prostate carcinoma has markedly improved.[1] However, an increasing number of radical prostatectomy specimens have minimal, potentially insignificant cancer, and these men may not have derived optimal benefited from definitive therapy.[2–4] Unilateral cryosurgery has recently been proposed and applied as a focal treatment for prostate cancer when on biopsy disease is confined to 1 prostate lobe.[5–8] However, prostate cancer is recognized as a multifocal and bilateral disease with previous



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studies showing on average 7.3 cancers per prostate.[3,9] Whether in the modern screening era these data are still valid and to what extent multifocal contralateral tumors left behind by focal therapy may be clinically insignificant have not been previously addressed to our knowledge.

## MATERIALS AND METHODS

We investigated 100 consecutive serially sectioned and completely embedded radical prostatectomy specimens where the needle biopsy predicted limited disease in the resection specimen (less than 3 positive cores, 50% or less involvement of any positive core, Gleason score 6 or less).[4] In addition, as 1 of the criteria for unilateral cryotherapy is that the biopsy cancer should be unilateral, all of the positive needle cores were restricted to 1 side of the gland. A total of 85 (85%) patients had normal digital rectal examinations (stage T1c) and the remaining 15 (15%) had clinical stage T2a disease with the palpable lesion on the side of the positive biopsy. Preoperative variables assessed were number of positive cores, percentage of tumor in each positive core, Gleason score in each positive core, patient age and preoperative serum PSA. As biopsies were performed elsewhere, detailed information on the number of cores sampled was not available, although biopsies were performed from 2005 to 2006 when extended sampling technique was routine. Similarly it is unknown how many of these cases had more than 1 biopsy before the diagnosis was made.

The 100 consecutive radical prostatectomy specimens were fixed in 10% neutral buffered formalin, serially sectioned in 0.3 cm slices, totally embedded and examined in their entirety histologically. All cases were reviewed by 5 genitourinary pathologists. Each tumor nodule was circled along the periphery and the volume was calculated using the grid method. Areas of the nodules that appeared on multiple slides were photocopied over a paper containing 1 mm squares. The number of squares that the tumor nodule occupied was counted. The volume of individual tumor nodule was recorded with a correction factor for fixation related shrinkage, that is, individual tumor nodule volume ($cm^3$) = number of squares of individual tumor nodule × 0.01 ($cm^2$) × 0.3 (cm, thickness of horizontal sections) × 1.12 (correction factor for fixation related shrinkage). Total gland tumor volume as well as tumor volumes on the side of and opposite the biopsy was calculated. The numbers of tumor nodules on the side and opposite to the biopsy were also counted.

The ability to predict radical prostatectomy tumor volume on the opposite side of the biopsy stratified by the number of positive cores (1 or 2) and maximum percentage of cancer per core were tested by Student’s t test and logistic regression analysis, respectively (StataCorp).

## RESULTS

Mean and median patient age was 58 years (range 40 to 70). Mean and median preoperative PSA was 5.5 and 4.8 ng/ml, respectively, with values of 4 or less in 37 (37%) cases, 4 to 10 in 53 (53%), greater than 10 in 7 (7%) and unknown in 3 (3%). Mean and median maximum percentage of the involved needle biopsy core was 13.9% and 10%, respectively (range 5% to 40%). The number of positive cores was 1 in 66 (66%) cases and 2 in 34 (34%) cases.

The mean and median number of separate tumor nodules within the entire prostate was 2.9 and 2.5, respectively, with a range of 1 to 9. The number of tumor nodules on the biopsy positive side ranged from 0 to 6 (0 in 3 cases, 1 in 49, 2 in 29, 3 in 12, 4 in 3, 5 in 3 and 6 in 1). Finding no tumor on the positive biopsy side in 3 cases likely reflects minute cancers sampled on biopsy which remained unsampled in the paraffin blocks despite serially sectioning and totally embedding the prostate. In 63 (63%) cases there were discrete tumor nodules in the radical prostatectomy restricted to the opposite side of the positive biopsy (1

in 26 cases, 2 in 25, 3 in 10 and 4 in 2). In 65 (65%) cases there was some tumor on the side opposite the positive biopsy, which included discrete tumor nodules restricted to the opposite side as well as tumor volume crossing over from tumor nodules primarily on the biopsy positive side.

Mean and median total tumor volume in the entire gland was 0.6 and 0.3 $cm^3$, respectively (range 0.003 to 3.3). The total tumor volume in the radical prostatectomy on the opposite side of the positive biopsy averaged 0.2 $cm^3$ (largest 1.3). In 23 (23%) cases the total tumor volume on the side opposite the positive biopsy was larger than that on the biopsy positive side. A total of 13 (13%) cases had clinically significant size prostate cancer (more than 0.5 $cm^3$) on the opposite side (table 1). Tumor volume on the side opposite from the positive biopsy could not be predicted by the number of positive cores (1 vs 2) or maximum percent of the core involved by tumor. In 7 of the 13 cases the tumor was predominantly located anteriorly with 6 mostly in the transition zone, and 1 in the anterior horn of the peripheral zone and the transition zone. Of the 13 cases all were organ confined on the side contralateral to the positive biopsy and 6 had Gleason score 3 + 4 = 7 tumor on the contralateral side.

Of the 87 cases with less than 0.5 mm on the side contralateral to the positive biopsy, extraprostatic extension was seen in 1 case and positive margins were seen in 2 cases (1 in an area of capsular incision) on the contralateral side. Gleason pattern 4 or 5 was seen in 7 cases contralateral to the positive biopsy (3 + 4 = 7 in 3 cases, 4 + 3 = 7 in 1, 4 + 4 = 8 in 1, 3 +5 = 8 in 1 and 4 +5 = 9 in 1 case). Adverse contralateral findings in these small foci reflected extension of tumor from the dominant nodule on the side of the positive biopsy. In total 20% of cases had some contralateral adverse pathology in terms of size, extraprostatic extension, grade or margins (table 2).

None of the 20 cases with contralateral adverse pathology had PSA values greater than 10 ng/ml. Of the 7 cases with serum PSA greater than 10 ng/ml 5 had no contralateral tumor, and the remaining 2 had contralateral organ confined, Gleason score 3 + 3 = 6 tumor measuring 0.04 and 0.11 cc, respectively.

## DISCUSSION

Definitive therapy for prostate cancer, whether with surgery or radiotherapy, intends to treat the entire prostate. The only variations of therapy that account for the dominant tumor are radical prostatectomy selectively sparing the neurovascular bundle on the side opposite the preoperatively biopsy detected tumor and brachytherapy placing extra radioactive seeds in the area of preoperatively biopsy detected tumor. The foundation for treating the entire prostate is that prostate cancer is a multifocal disease. Studies done before the PSA screening era demonstrated that on average there were 7.3 (median 4, range 1 to 60) cancers per prostate, with multifocal adenocarcinoma of the prostate present in more than 85% of prostates.[9,10] It was recognized even in this earlier era that multifocal cancers were often small, potentially insignificant cancer. In the study by Bastacky et al the mean number of significant tumor nodules (0.5 $cm^3$ or greater) was 1.7 whereas multifocal tumor nodules less than 0.5 $cm^3$ were more than 3 times as common.[9] In another study 80% of multifocal prostate cancers, excluding the preoperatively detected dominant tumor, were smaller than 0.5 $cm^3$.[3]

With PSA screening and more extensive biopsy sampling there has been an increase in the resection of prostates harboring potentially insignificant cancers. Although the majority of stage T1c cancers are significant tumors warranting definitive therapy, approximately 25% of these tumors detected by needle biopsy are thought to be insignificant tumors.[4] In

approximately 5% of radical prostatectomy specimens tumors are so small that they are histologically difficult to identify.[2,11]

With the recognition that we are detecting earlier, more limited prostate cancer in the modern era, new approaches to treat prostate cancer have included localized prostate cancer therapy. Unilateral cryosurgery has been proffered as a method to treat prostate cancer thought to be confined to 1 prostate lobe based on biopsy findings. The potential advantages of focal therapy include improved quality of life with greater preservation of potency and urinary continence.[5–8] However, the greatest concern with focal cryosurgery is that significant cancer will remain untreated on the side opposite the therapy.

In a recent study of 1,386 radical prostatectomies 18.3% had unilateral cancer. The majority of unilateral tumors (72%) were low volume occupying less than 5% of the gland. The authors concluded that only a select group of men diagnosed with prostate cancer have completely unilateral cancers that would be amendable to focal ablation therapy targeting 1 lobe. Because in a minority of cases from this study the prostates were not totally submitted for histological examination the percentage of unilateral cancers may have even been less (Polascik, personal communication). Several studies have tried predict unifocal disease. Djavan et al found that unifocal disease constituted 33% of their cases, and could be reliably differentiated from multifocal disease with a sensitivity of 90% using transition zone PSA density and free/total PSA.[12] In recent study a negative 5-core biopsy on 1 side of the gland underdiagnosed prostate carcinoma in 54% and underdiag nosed clinically significant prostate carcinoma in 11% of the hemi-prostates.[1] Most of the clinically significant cancers that were not detected on biopsy were in the anterior horn of the peripheral zone and transition zone.

In the current study we selected potentially ideal candidates for focal therapy using the same biopsy criteria to select men who are likely to have insignificant cancer in our active surveillance program. The only differences were in the current study the entire biopsy tumor had to be restricted to 1 side the gland and we did not factor in serum PSA density levels Although 7 patients had PSA values greater than 10 ng/ml and might not have been selected for unilateral ablation, none these patients had adverse pathology on the contralateral side such that including them did not bias the data against limited cryotherapy. The stringency of these criteria was evidenced a low overall tumor volume with a median of 0.3 $cm^3$. Our criteria are more restricted than those that have been used select men for focal cryotherapy. Onik[5] and Bahn et al[6] required unilateral cancer on initial biopsy before focal cryotherapy. In the Onik study re-biopsy was performed in the area the previously negative biopsy consisting of 5 cores from the lateral peripheral zone and 3 cores from the medial transition zone. Bahn et al performed targeted biopsy of any suspect lesions seen on ultrasound. In both of these studies no restriction was made based on the Gleason score or the extent of cancer on the positive biopsies. Lambert et al had biopsy criteria for focal cryotherapy similar to those in our study with 1 or 2 positive unilateral cores in 1 or 2 contiguous biopsy cores with a tumor volume less than 10% in a 12-core biopsy.[8] In their article they stated that all cases had less than 50% tumor volume in the positive cores. However, in this study Gleason score 3 + 4 = 7 cancers on biopsy were eligible along with lower grade tumors.

A potential weakness of this study is that extraordinary steps were not taken to preoperatively identify contralateral tumor, as may have occurred if these patients were candidates for focal cryotherapy. Other imaging aids such as color or power Doppler, dynamic magnetic resonance imaging, spectroscopy, special 3-dimensional ultrasound reconstruction software and nuclear imaging were not used to try to identify contralateral tumor. However, it has not been proven that these techniques are more sensitive and specific than standard imaging studies. Many clinicians are performing additional biopsies on the

untreated side. Therefore, if a clinician performs at least 12 cores on the uninvolved side, it may pick up occult cancer present, thereby excluding some patients from ablation. Followup biopsies would have an increased chance of detecting occult cancers in the untreated side (the active surveillance side) and these patients would then be considered for additional therapy. Nonetheless, it is unlikely that all of the significant contralateral tumor identified in the current study would have been detected with additional studies, as in some cases the tumor volume was small yet other factors were adverse (table 2).

## CONCLUSIONS

The data from our study can be used by proponents as well as opponents of focal therapy. Those with a favorable view of focal therapy can note that only a minority of men would have been undertreated for whom conventional therapy could have been curative. Opponents would argue that even using stringent selection criteria 20% of the men who would have undergone focal cryotherapy would have had potentially significant prostate cancer that would have not been treated. An unanswered question is how many more men who had contralateral tumor that was less than 0.5 cc may have had progression with adverse outcomes over time. In 65% of cases there was some contralateral tumor to the positive biopsy side, taking into account extension of tumor from the positive biopsy side as well as distinct contralateral tumor nodules. Urologists need to be informed and patients should be told the risks of leaving cancer behind before undergoing this experimental therapy.

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## Abbreviations and Acronyms

| | |
|---|---|
| **OC** | organ confined |
| **PSA** | prostate specific antigen |
| **PZ** | peripheral zone |
| **TZ** | transition zone |

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## Table 1

Cases with more than 0.5 cc of tumor contralateral to positive biopsy site

| Case No. | Grade | Predominant Location |
|---|---|---|
| 1 | 3 + 3 = 6 | Anterior (TZ) |
| 2 | 3 + 3 = 6 | Anterior (TZ) |
| 3 | 3 + 3 = 6 | Anterior (TZ) |
| 4 | 3 + 3 = 6 | Anterior (anterior horn + TZ) |
| 5 | 3 + 3 = 6 | Posterior (PZ) |
| 6 | 3 + 3 = 6 | Posterior (PZ) |
| 7 | 3 + 3 = 6 | Posterior (PZ) |
| 8 | 3 + 4 = 7 | Anterior (TZ) |
| 9 | 3 + 4 = 7 | Anterior (TZ) |
| 10 | 3 + 4 = 7 | Anterior (TZ) |
| 11 | 3 + 4 = 7 | Posterior (PZ) |
| 12 | 3 + 4 = 7 | Posterior (PZ) |
| 13 | 3 + 4 = 7 | Posterior (PZ) |

All cases stage OC, negative margins.

## Table 2

Cases with less than 0.5 cc of tumor yet adverse pathology contralateral to positive biopsy site

| Case No. | Stage | Margins | Grade |
|---|---|---|---|
| 14 | OC | Neg | 3 + 4 = 7 |
| 15 | OC | Neg | 3 + 4 = 7 |
| 16 | OC | Neg | 3 + 4 = 7 |
| 17 | OC | Neg | 4 + 4 = 8 |
| 18 | OC | Neg | 3 + 5 = 8 |
| 19 | Capsular incision | Pos | 4 + 3 = 7 |
| 20 | Extraprostatic extension | Neg | 4 + 5 = 9 |