Prediction of tumor stage and lymph node involvement with dynamic contrast-enhanced MRI after chemoradiotherapy for locally advanced rectal cancer.

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Abstract

Purpose

The usefulness of restaging by MRI after chemoradiotherapy (CTxRTx) in patients with locally advanced rectal cancer has not yet been established, mostly due to the difficult differentiation between viable tumor and fibrosis. MRI with dynamic contrast-enhanced (DCE) sequences may be of additional value in distinguishing malignant from non-malignant tissue. The aim of this study was to assess the accuracy of tumor, nodal staging and CRM involvement by MRI with DCE sequences after CTxRTx.

Methods

The accuracies were assessed by MRI on T2-weighted MR images with DCE sequences in patients with locally advanced rectal cancer after long course CTxRTx. MR images were assessed by two independent radiologists.

Results

For tumor staging and CRM involvement, MRI with DCE sequences had an accuracy of 45% and 60%, respectively. The accuracy for nodal staging was 93%. On MRI, malignant lymph nodes had a median diameter of 8 mm (range, 4 – 18 and benign lymph nodes a median diameter of 4mm (range, 3 – 11). A significant indicator for benign nodes was hypointensity on T2 weighted images *(p* < 0.001) and early complete arterial phase enhancement on dynamic contrast-enhanced weighted images *(p* < 0.001). A significant indicator for malignant nodes was heterogeneity on T2 weighted images (χ^2 *p* < 0.000) and early incomplete arterial phase enhancement on dynamic contrast-enhanced (*p* < 0.001).

Conclusions

MRI with DCE is a useful tool for nodal staging after CTxRTx. The addition of DCE sequences did not improve the accuracy of determining the tumor stage, CRM involvement and in detecting complete response.

Introduction

Colorectal cancer is the third most common cancer among men and women worldwide.[1] Rectal cancer accounts for 30% of these colorectal malignancies. Surgery with total mesorectal excision (TME) is the cornerstone of treatment in rectal cancer and has led in combination with neo-adjuvant radiotherapy to a decrease in local recurrences.[2-4] Predictive factors for recurrence are depth of tumor invasion, number of malignant lymph nodes and involvement of the circumferential resection margin (CRM).[4,5] Therefore, patients with locally advanced rectal cancer (e.g. large T3 or T4 tumors or involved lymph nodes) have a higher recurrence rate. Currently, these patients are usually treated with long course radiotherapy in combination with chemotherapy followed by TME or multivisceral resections.[2,3,6,7]

Magnetic Resonance Imaging (MRI) is the most accurate imaging modality for assessment of T-stage and CRM for locally advanced tumors. MRI can accurately predict an involved CRM and the transmural invasion of the tumor.[8-10] An involved CRM is a reason to administer long course chemoradiotherapy (CTxRTx). Nodal disease may also be a reason to administer CTxRTx. However, nodal disease remains a difficult radiologic diagnosis.[11] New techniques such as high spatial MRI and ultra-small particles iron oxide (USPIO) enhanced MRI showed promising results in the detection of nodal involvement.[12,13]

The usefulness of restaging after CTxRTx by MRI has not yet been established. After CTxRTx the tumor can be downstaged to 60% and approximately 20% of the tumors show a pathological complete response (pCR).[14,15] Additional imaging may render the patient, in case of downstaging and N0 status, operable with a less extensive resection. On the other hand, in patients in whom the CRM is still involved, more aggressive surgery is justified. Unfortunately, the accuracy of MRI after CTxRTx in predicting tumor and nodal stage is poor, mostly due to the difficult differentiation between viable tumor and fibrosis.[11,16-18] Dynamic Contrast-Enhanced (DCE) MRI may be of additional value in distinguishing malignant from non-malignant tissue. Malignant tissue shows specific contrast-enhanced patterns due to the neoangiogenesis, which gives elevated perfusion and permeability, in patients without neo-adjuvant therapy.[19] The aim of this study is to assess the accuracy of DCE MRI with DCE sequences for tumor, nodal staging and CRM involvement after CTxRTx in patients with locally advanced rectal cancer.

Methods and Materials

Patients

Between June 2005 and March 2009, 101 patients with locally advanced rectal cancer were treated with neo-adjuvant long course radiotherapy followed by rectal surgery. Thirty-three patients were treated by radiotherapy without chemotherapy and 13 patients were restaged in the referring hospital, leaving 55 patients treated with CTxRTx, who were all restaged by MRI with DCE sequences.

All patients had biopsy proven adenocarcinoma of the rectum within 15 cm of the anal verge. Locally advanced rectal cancer was defined on imaging prior to the chemoradiatherapy. According to local standard of care, tumors greater than 5 cm at colonoscopy (clinically large T3), a clinically fixed tumor, tumor invasion in an adjacent organ, tumors with an involved CRM (margin <2 mm) and node positivity (lymph node larger than 8 mm on CT-scan or MRI) were considered as locally advanced rectal cancer.

All patients were evaluated including a complete history and physical examination, colonoscopy, tumor biopsy, computed tomography (CT) scan of the abdomen, magnetic resonance imaging (MRI) of the pelvis and a chest X-ray or chest CT scan.

Therapeutic regimen

Capecitabine was administered orally at a dose of 825 mg/m2 twice a day during radiotherapy days. The first daily dose was given two hours before radiotherapy and the second dose twelve hours later. Patients received a dose of 50-52 Gy radiotherapy delivered in 25-26 fractions of 2.0 Gy. Radiotherapy was administered by a three-field technique, using one posterior and two lateral beams, a four-field box or with five fields using intensity modulated radiotherapy.[7]

Radiology

Imaging was performed after CTxRTx after median interval of 5 weeks (interquartile range, 4 – 6). Magnetic resonance imaging was performed using thin-section (3 or 5 mm) high-spatial resolution, phased array coils on a 1.5 T MR systems (Siemens Vision, Erlangen, Germany; Philips Intera, Best, The Netherlands). Patients were scanned supine without gastro-intestinal tract preparation, rectal insufflation or relaxants. The following sequences were used in all patients: transverse, coronal and sagittal Surv Haste (TSE, 18877/100, 90°), transverse T2W (TSE, 4661/80, 90°), transverse T2W/ Spir (TSE, 4586/80, 90°), transverse T1W (FFE in/out, 184/2.3- 4.0, 80°), transverse Sense Dyn (TFE, 136/1.16, 90°), transverse and sagittal 3D TFE (TFE, 3.4/1.68, 15°).

Dynamic imaging was performed before and after intravenous injection of 20 ml of gadopentetate dimeglumine in the arterial dominant, venous dominant and 2-minute delayed phases.

Image interpretation

All images were assessed by a radiologist prior to surgery for determination of the operation strategy. Surgery was performed with a median of 4 weeks (interquartile range, 3-5) after restaging. Two radiologists: reader 1 (R.D.) and reader 2 (F.W.) retrospectively assessed all images independently. Both readers had over 5 years of experience in rectal cancer imaging and were blinded to the pathologic and surgical findings. The following parameters were recorded by the readers:

Tumor stage

The distance of the lower and upper border of the tumor to the anal verge, maximum axial diameter, CRM, T-stage and tumor invasion, for T2-weighted images and Dynamic contrast-enhanced images were assessed.

Nodal stage

N-stage was determined by location, size (only nodes >3 mm were evaluated), shape (round or oval), border (irregular or sharp), signal intensity (SI) on T2 weighted images (hyperintens, hypointens SI) and homogeneous or heterogeneous SI. On dynamic contrast-enhanced images the arterial phase (early or late and complete or incomplete) and possible washout effects (complete or incomplete) were evaluated. Criteria for suspect malignant lymph nodes were size ≥ 5 mm, round shape, irregular border, heterogeneity on T2 images and incomplete arterial phase and washout effects.[20,21] A lymph node was considered malignant when ≥ 3 criteria were positive.

Circumferential Resection Margin (CRM)

An involved CRM was defined as a margin ≤2 mm to the mesorectal fascia or in case of tumor invasion through the mesorectal fascia into surrounding structures.

Surgery and histopathology

Total mesorectal excision was performed in all patients. In patients whose circumferential resection margin (CRM) were considered at risk (CRM <2mm) intraoperative radiotherapy (IORT) was applied. [4,22] Pathologic examination of the histology specimen was evaluated according to the protocol of Quirke et al. [23] The report noted the depth of tumor invasion into the bowel wall and surrounding tissue, differentiation grade of the tumor, lymph node involvement and resection margin involvement.

Radiologic-pathologic comparison

The tumor, nodal status and CRM involvement determined by MRI were compared to pathologic staging of the surgical specimen.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 15.0. The data used when appropriate were mean, median, (interquartile) range and standard deviation. The diagnostic accuracy, sensitivity, specificity, negative predictive and positive predictive value of MRI was computed in determining the post-chemoradiation nodal stage. The interobserver agreement was calculated by using K statistics. K values of less than 0 indicated poor agreement, 0-0.20 indicated slight agreement, 0.21-0.40 indicated fair agreement, 0.41-0.60 indicated moderate agreement, 0.61-0.80 indicated substantial agreement and 0.80-1.00 indicated almost perfect agreement. The χ^2-test was used to determine the correlated factor to predict the nodal positivity, if the assumption of adequate cell sizes (≥5) was not met; the Fisher's exact test was applied. The results are significant at a *P*-value of less than 0.05.

Results

Surgery and histopathology

Surgery was performed in 41 males and 14 females with a median age of 61 years (range 33 – 78) The median interval of surgery after CTxRTx was 9 weeks (interquartile range, 8 – 10) Surgical and pathologic characteristics are depicted in *table I*.

Table I. Characteristics of 55 patients with locally advanced rectal carcinoma after CTxRTx

	Number of patients (%)
Surgery	
LAR	25 (46)
APR	20 (36)
Total exenteration	4 (7)
Posterior exenteration	6 (11)
Tumor staging	
T0	6 (11)
Tis	2 (4)
T1	0 (0)
T2	10 (18)
T3	32 (58)
T4	5 (9)
Nodal staging	
N0	45 (82)
N1	5 (9)
N2	5 (9)

LAR, Low anterior resection; APR, abdominoperineal resection

A pathological complete response was found in 6 (11%) patients. Five patients underwent a resection with viable tumor within 1 mm of the CRM. One patient had a positive lymph node <1 mm from the mesorectal fascia. Four patients received IORT after resection due to CRM of <2 mm. [22] In resection specimens a median of 9 (range 1 – 21) lymph nodes were retrieved. Ten (8,8%) patients had a total of 42 tumorpositive lymph nodes.

Radiologic-pathologic comparison

A comparison of preoperative MRI staging and histopathological staging for both readers is depicted in *table II.*

Tumor stage

The readers both understaged 4 (7%) patients. Reader 1 had an accuracy of 40% (22 patients) and overstaged 29 (53%) patients. Reader 2 had an accuracy of 45% (25 patients) and overstaged 26 (47%) patients. The k statistics show fair agreement (k = 0.37) for T-staging.

Table II. Comparison of T-staging by DCE MRI and histopathology

		Histopathology					
		T0	**Tis**	**T2**	**T3**	**T4**	
Reader 1	T2	3	1	3	3	0	10
	T3	3	1	6	15	1	26
	T4	0	0	1	14	4	19
	Total	6	2	10	32	5	55
Reader 2	T2	0	0	4	3	0	7
	T3	5	1	5	17	1	29
	T4	1	1	1	12	4	19
	Total	6	2	10	32	5	55

Nodal stage

The accuracy of both readers in nodal staging is noted in *table III*. Both readers accurately diagnosed the same 8 patients node positive on MRI. The accuracy for reader 1 for nodal staging 89%, sensitivity 80%, specificity 91%, a positive predictive value (PPV) of 66% and a negative predictive value (NPV) of 95%. Reader 2 showed an accuracy of 93%, sensitivity of 80%, specificity of 96%, a PPV of 80% and a NPV of 96%. K-statistics showed almost perfect agreement (k = 0.89).

Table III. Comparison of N-staging by DCE MRI and histopathology

		pN0	pN+	
Reader 1	cN0	41	2	43
	cN+	4	8	12
	Total	45	10	55
Reader 2	cN0	43	2	45
	cN+	2	8	10
	Total	45	10	55

Characteristics of lymph nodes

The median diameter of the lymph nodes was as follows: malignant lymph nodes 8.1 mm (range 4.2 - 16.2) and 8.0 mm (range 4.0 - 18.0) for reader 1 and 2 respectively, benign lymph nodes 4.8 mm (range 3.0 – 11.0) and 4.4 mm (range 3.0 - 11.0) for reader 1 and 2 respectively.

Circumferential resection margin (CRM)

The accuracy of both readers in predicting CRM involvement is depicted in *table IV.* The accuracy for reader 1 was 60%, sensitivity 86%, specificity 49%, PPV of 38% and a NPV of 91%. Reader 2 showed an accuracy of 56%, sensitivity 79%, specificity 48%, PPV of 34% and a NPV of 91%. K-statistics showed moderate agreement (k = 0.59) for predicting CRM involvement.

Table IV. Comparison of CRM involvement by DCE MRI and histopathology

		Histopathology CRM involved	CRM not involved	
Reader 1	CRM involved	12	20	32
	CRM not involved	2	21	23
	Total	14	41	55
Reader 2	CRM involved	11	21	32
	CRM not involved	3	20	22
	Total	14	41	55

CRM; Circumferential resection margin

There was a significant difference in shape of malignant and benign nodes. Reader 1 showed that a round shape is associated with benign nodes (p=0.026) and reader 2 showed that an oval shape is associated with benign nodes (p=0.008).

The border of lymph nodes did not give a significant difference in the assessment of lymph nodes for reader 1, but reader 2 showed that a sharp border is associated (p=0.005) with benign nodes. Concerning hyperintensity on T2 weighted images, both readers found no significant differences. Hypointensity was an significant indicator for benign nodes (reader 1 p=0.000; reader 2 p=0.000) and heterogeneity was an

significant indicator for malignant nodes (reader 1 p=0.000; reader 2 p=0.000) for both readers.

There were no washout effects detected and only the following characteristic on DCE images gave a significant difference for both readers; early complete arterial phase *(Fig I.)* was a significant characteristic of benign nodes (reader 1 p=0.000; reader 2 p=0.000). Early incomplete arterial phase (*Fig II.)* was a significant characteristic of malignant nodes (reader 1 p=0.000; reader 2 p=0.000).

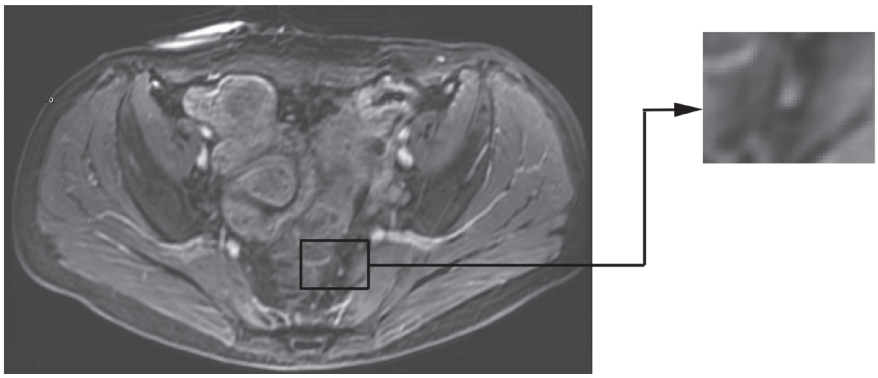

Figure I. DCE-weighted image with early complete arterial phase

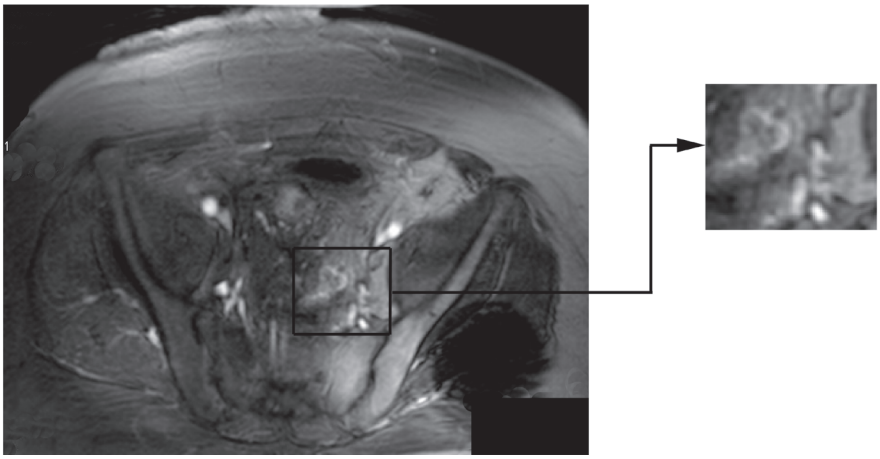

Figure II. DCE-weighted image with early incomplete arterial phase

Interval between CTxRTx, surgery and restaging

The accuracy of tumor and nodal staging in patients having surgery <9 weeks after CTxRTx compared to patients having surgery ≥9 week was not significantly different. The accuracy of tumor staging was 42% vs. 37% (p=0.85) and the accuracy of nodal staging was 87% vs. 92% (p=0.53), The accuracy of tumor and nodal staging when

restaging was performed <4 weeks compared to ≥4 weeks prior to surgery was not significantly different either. The accuracy of tumor staging was 29% vs. 46% (p=0.08) and the accuracy of nodal staging 92% vs. 87% (p=0.53)

Discussion

This study was conducted to evaluate the additional value of MRI with DCE sequences in restaging after CTxRTx in patient with locally advanced rectal cancer. Although the accuracy for T-stage was poor, the addition of DCE sequences showed a high accuracy in detecting malignant lymph nodes. Complete arterial phase on DCE was a significant indicator for benign nodes and incomplete arterial phase (enhanced rim) was significant for malignant nodes. Complete pathologic response, carcinoma in situ and T1 stage tumor could not be correctly detected.

The addition of DCE to determine T-stage after CTxRTx has not proven its usefulness in this study. The poor accuracy of the T-stage could be explained by the fact that rectal cancer has a high level of maturation of vessels, which show relatively low permeability, thus less enhancement on DCE MRI.[24] The accuracy of MRI for T-stage was 45% in this study. Other studies, using MRI with additional DCE sequences showed accuracies of 44-77%.[16,25,26] However, these studies divided patients into two T-stages to define accuracy (T0 vs. >T1 or T0-2 vs. T3-4).[16,25] MRI without additional DCE sequence, showed comparable accuracy results of 34-60%.[18,27-31]

The poor accuracy in predicting T-stage and CRM after CTxRTx is in great contrast to the high accuracy of MRI-staging in patients with rectal cancer treated without neo-adjuvant CTxRTx. A recent meta-analysis reported a sensitivity and specificity in tumor staging of 87% and 75% in patients treated without neo-adjuvant CTxRTx.[32] The tendency of post-chemoradiotherapy MRI to overstage the T-stage and CRM involvement was reported previously and may be caused by the inability of MRI to distinguish between viable tumor cells and fibrosis. Recently, Patel et al. analysed the value of MRI after CTxRTx in rectal cancer patients to analyse good versus poor responders with the histopathological standards of T stage (ypT) and tumor regression grading (TRG). Even using only 2 different t-stages (T0-T3a vs. T3b-4) 19% of the patients were under- or overstaged.[33]

The time span from the end of chemoradiotherapy to surgery has slowly increased over the years. Delaying surgery may reduce postoperative morbidity without compromising prognosis.[34] Moreover, several studies showed a higher percentage of pathological complete response and downstaging after a longer interval between ending CTxRTx and surgery.[35-37] This downstaging effect may influence the accuracy of the restaging MRI. However, we found no differences in accuracies of tumor and nodal staging between

patients in whom surgery was performed < 9 weeks or ≥9 weeks after ending CTxRTx. In addition, it has been suggested that the restaging by MRI shortly before surgery may improve the accuracy of tumor staging.[38] In our study restaging was performed with a median interval of 4 weeks before surgery. We found no higher accuracy of tumor and nodal staging for patients restaged <4 weeks compared to patients restaged after ≥ 4 weeks.

The addition of DCE to high-spatial MRI showed a high accuracy in nodal staging compared to other studies that also applied DCE. They reported accuracies of 62-65%.[16,25,26] This difference could be explained by the fact that we included different enhancement patterns to distinguish between benign and malignant nodes. One study staged a node malignant if it was bigger than 5 mm,[16] while the other 2 studies did not describe any criteria for malignant nodes.[25,26] Studies without additional DCE sequences reported accuracies of 68-71%.[28,31] One study only used the criteria > 5 mm to stage a node malignant while the other study did not note any criteria for malignant nodes. Brown et al.[21] reported that by assessing morphologic features of lymph nodes on MRI, malignant nodes can be detected with a greater degree of sensitivity and specificity compared to nodal size measurement. Studies using the morphologic criteria stated by Brown in addition to size cut-off values (> 5mm mesorectal, > 10mm extramesorectal) still showed lower accuracies of 70-78%.[27,29] Accuracies were even lower even when cut-off values were not used 75-88%[39-41]. We used the same morphologic features described by Brown et al. with a cut-off value of >3 mm. Approximately 9% of the malignant nodes are missed on MRI with a cut-off value of 3 mm in patients treated without neo-adjuvant therapy.[20] Recently, prospective assessment of imaging with MRI without DCE after preoperative chemoradiotherapy for rectal cancer showed an accuracy for nodal staging of 68% with a NPV of 78%.[30] MRI with ultra small particles iron oxide showed promising results for nodal staging with a sensitivity of 93% and a specificity of 96% when an estimated area of white region within the node that was larger than 30%.[13] This sensitivity and specificity were slightly higher than in our study. However, the study mentioned above excluded all patients who were treated with chemoradiotherapy. Therefore, these results may not be comparable to ours.

The accuracy of MRI with DCE for nodal stage was 93% with a PPV of 80% and a NPV of 96%. There was good agreement between the two readers. Nonetheless, both missed the same two histopathology node positive patients. In one patient no benign or malignant nodes were detected on MRI. In the other patient, two nodes were detected, which were staged benign on MRI with confirmation on histopathology. However, the tumor incarcerated a malignant node, undetectable on MRI. Even with the knowledge of the presence of malignant lymph nodes, both radiologists were not able to detect any suspect lymph nodes after reassessment of the MRI.

Two histopathology node negative patients were overstaged by both readers. In these two patients nodes had an axis of more than 8 mm (9.0 mm and 11.0 mm, respectively). Although the median diameter of the malignant nodes was bigger than that of the benign nodes in this study (8.0 and 4.4 mm respectively), it shows size is not a single reliable criteria to diagnose malignant nodes, which was confirmed in results by other studies.[20,21]

MRI with DCE has a good predictive value for malignant nodes. Generally, complete early arterial phase was a significant indicator of benign nodes, whereas incomplete arterial phase was a significant predictor of malignant nodes. Malignant nodes showed an intense border and hypointense core on DCE. This difference in intensity could be explained by that as tumors grow in size, their metabolic demands become too great for existing vasculature. At this stage, the centre of the mass becomes necrotic, leading to the common situation of a necrotic core and an active tumor periphery. This finding has been previously described in patients with a squamous cell carcinoma of the head or the neck. MRI with additional DCE sequences showed significantly different results in contrast intensity for their core and rim in malignant cervical lymph nodes. Benign nodes did not show significant differences, which is in concordance with our findings.[42]

Complete pathologic response, carcinoma in situ and T1 stage tumor could not be correctly detected on MRI even with the addition of DCE sequence. MRI with DCE sequences showed similar poor results in predicting pCR compared to conventional MRI. Predicting pCR after CTxRTx can be of great value for patients with rectal cancer. Patients could be spared unnecessary surgery with high morbidity. Promising results in predicting pCR are shown in adding diffusion weighted (DW) MRI to conventional MRI. Their diagnostic accuracy for the evaluation of pCR increased to 85%.[14,43,44]

Due to the retrospective nature of this study, we were not able to directly assess whether lymph nodes detected on MRI are the same lymph nodes assessed with histopathology. With prospective research a node-by-node correlation is capable to accurately link lymph nodes detected on MRI with DCE to lymph nodes retrieved at histopathology. Another drawback is the relative small amount of patients included in this study. Many of our patients were restaged by MRI without additional DCE sequences and therefore could not be included in this study.

In conclusion, the addition of DCE sequences improved the accuracy of nodal staging after chemoradiotherapy. However, additional DCE sequences did not improve the accuracy for tumor staging, CRM involvement or detecting a pathological complete response. In our opinion, the addition of DCE sequences is a significant step forward towards more accurate staging by MRI after chemoradiotherapy. We think that further development and introduction of such highly accurate preoperative staging modalities will enable us to identify those patients who are candidates for less invasive surgery for rectal cancer or even for watchful waiting.

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