

RADIOTHERAPY OR SURGERY FOR PROSTATE CANCER?

Ten and fifteen-year results of external beam therapy

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Abstract

Ten and 15-year outcome results are reviewed that demonstrate the role of radiation therapy in the management of prostate cancer. Patients with favorable T2a (B1) cancers of unknown nodal status are shown to have equal 15-year survival whether treated with external beam radiation therapy or radical prostatectomy. Patients of unknown nodal status treated for T2b (stage B2) cancer with external beam radiation therapy show superior survival and disease-free survival when compared to results with radical prostatectomy. The role of radical prostatectomy in these patients is unproven. Patients with lymph node dissection negative clinical stages T1b (A2) and T2 (B) treated with external beam radiation therapy exceed their expected survival at 10 years (65% vs 60%), and 70% are free of any failure at 10 years with the majority of failures due to metastasis, not local disease. Similar results are obtained in selected surgical centers with radical prostatectomy in highly selected patients. Patients with stage T3, 4 (stage C) prostate cancer show 10 and 15-year survivals that offer curative therapy and hope to patients with these locally advanced cancers. No long-term data support a role for radical prostatectomy in these patients.

Key words: Prostate cancer, external beam radiotherapy, radical prostatectomy, long-term results, review.

The USA national averages demonstrate the successful transfer of external beam radiation therapy technology to the country as a whole, while no similar data are available to indicate the successful nationwide application of radical prostatectomy, particularly the nerve-sparing modification.

External beam radiation treatment of prostate cancer was begun in the USA in the late 1950s by Bagshaw et al. (1), George et al. (2) and del Regato (3). During the 1960s and 1970s irradiation was the predominant form of curative therapy although more than one-half of all patients were not treated with curative intent (4). Only a small fraction were treated with radical prostatectomy (4).

The 1980s were a time of change in urologists' attitudes about treatment of the disease with surgery, due in part to training more urologists in radical prostatectomy, the popularization of the retropubic approach and the development of the 'nerve-sparing' procedure with a potential for preserving potency (5, 6). No doubt the empiric bias of urologic surgeons that surgery was better played a role just as it did with general surgeons in slowing progress in the management of breast cancer.

Non-randomized studies

The problem of T2b (B2) cancer

The definition of what patient was a suitable candidate for radical prostatectomy was changed during the last 10 years and expanded to include patients with large nodules, bilobar stage B disease and some patients with poorly differentiated cancers without any long-term survival data to indicate a reason for change (7, 8). Based on outcome of their patients Elder et al. (9) regarded it unwise to recommend radical surgery for all men with T2b (B2) disease based on outcome in their patients. The reason for this recommendation was that 2/3 of their patients proved to be pathologic stage C and the 15-year survival was less than 13%. Catalona & Biggs (7) came to similar conclusion based on their extensive well-reported experience with radical prostatectomy. Table 1 shows that some contemporary

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Table 1
Pathologic observations in B2/PD cancer

Author (ref. No)	Total No.	No. B-2	Adverse features*	No. PD	Adverse features*
Eggleston & Walsh (8)	100	22	15 (68%)	9	?
Catalona & Biggs (7)	250	115	76 (66%)	32	25 (78%)
Pontes, 1990	?	158	84 (53%)**	-	-

*Positive margins, extensive periprostatic, positive seminal vesicles, positive nodes (microscopic).

**Positive margins only.

PD = Poorly differentiated.

radical prostatectomy series include large numbers of T2b (stage B2) patients and some poorly differentiated tumors, and it also shows that the identical pathologic observations are true in prostate cancer in the 1980s as was true in Jewett's patients where 66% were pathologic T3, 4 (stage C). I suspect time will show a similar poor long-term survival (<13%).

Radiation therapy series have 15 and 20-year results demonstrating superior outcome to the surgical treatment of T2b (B2) localized prostate cancers for patients of unknown lymph node status two of which are included as examples. Fig. 1 shows Bagshaw's long-term freedom from relapse for the Stanford system T2 or larger stage B patients (10). Thirty-three percent are free of relapse at 15 years. Fig. 2 shows Perez' data with 61% survival at 10 years (11). These superior long-term outcomes show why the patient with T2b (B2) disease should be treated with radiation therapy.

Fifteen-year survival for T2A (B1) prostate cancer

Fig. 3 compares the 15-year survival outcome of T2a (B1) cancer treated at Stanford (n = 134) with radiation, Mason Clinic (n = 195) with perineal prostatectomy and Johns Hopkins (n = 57) with perineal prostatectomy (10, 12-14). The first 2 are actuarial analysis while the

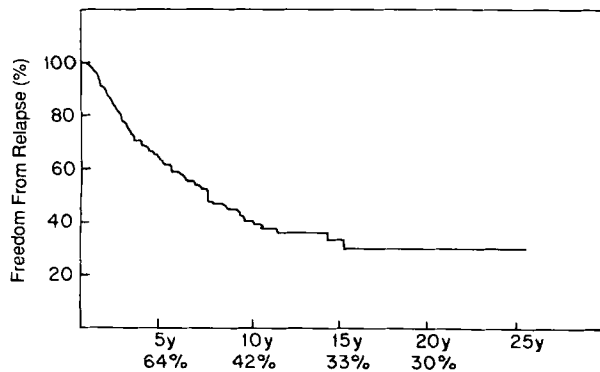


Fig. 1. Relapse-free survival for T2 prostate cancer treated with radiation. Stanford series, 183 patients. (Modified from Bagshaw et al. NCI Monogr 1988; 7: 47-60.)

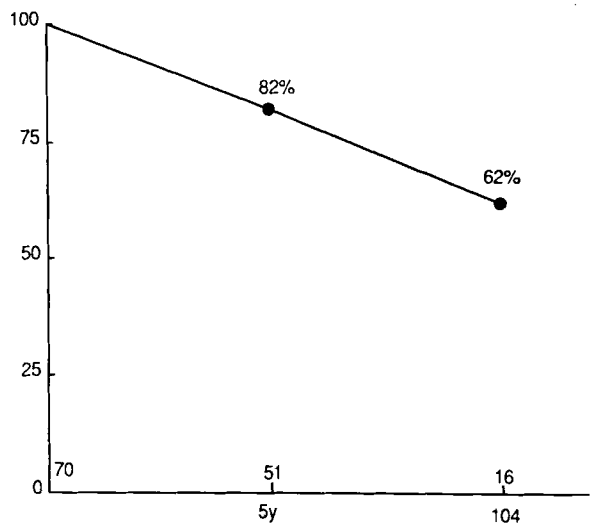


Fig. 2. Survival of T2 (B2) prostate cancer treated with radiation. (Modified from Perez et al. NCI Monogr 1988; 7: 85-94.)

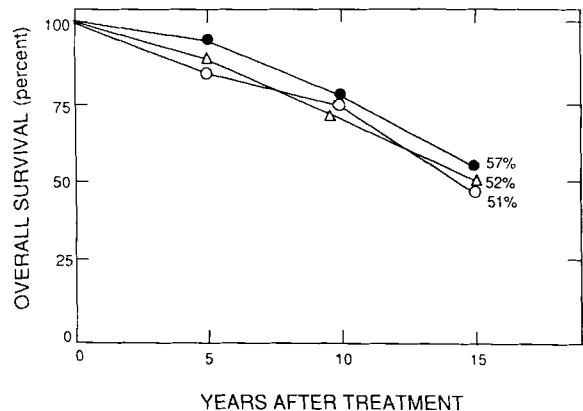


Fig. 3. comparison of 15-year survivals after treatment of B1 prostate cancer. (○) Johns Hopkins Hospital, 57 patients; (●) Virginia Mason Medical Center, 195 patients; (Δ) Stanford University, 134 patients. (Modified from Hanks Suppl. to Urol 1989; 23: 21-6.)

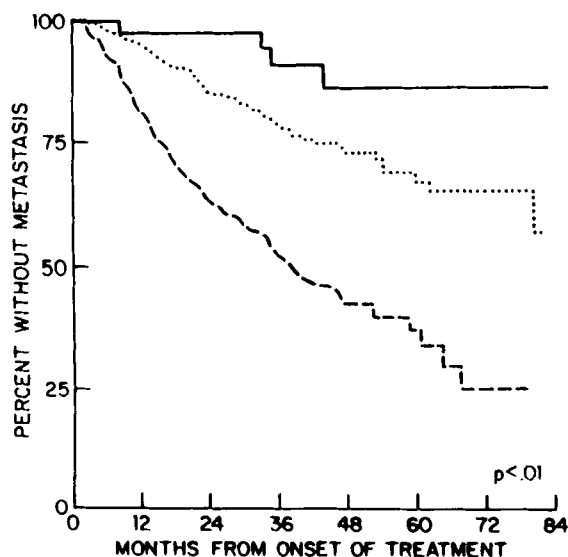


Fig. 4. Relation of prostate cancer Gleason score to metastasis — Gleason score 2-5; ···· Gleason score 6-7; - - - Gleason score 8-10. (Modified from Pilepich NCI Monogr 1989; 7: 61-6.)

Hopkins is absolute 15-year survival with lost patients eliminated from analysis. There is no difference in these favorable patients treated by either method, all of whom are of unknown lymph node status.

These series cannot really be compared as one does not know the distributions of significant prognostic indicators (particularly grade). Certainly, radiotherapy series include patients of all states of health and all grades of cancer while surgical series do not. Fig. 4 is an example of the difference in metastasis for T1b (stage A2) and T2 (stage B) patients of different grade in the RTOG (15). Overall results are determined by the distribution of grade.

Ten-year local control with external beam radiation therapy

Table 2 illustrates the success in long-term clinical local control with external beam radiation therapy. The PCS data are from national surveys conducted on patients

Table 2

Local control of prostate cancer by external beam radiation

Data source	Actuarial 5 year (%)	Free of local recurrence 10 year (%)
PCS national surveys		
A	97	97
B	86	74
C	75	69
RTOG prospective trials		
A	98	98
B	89	77
C	81	67

Table 3

Stanford post external beam radiation therapy biopsies J Urology, August, 1989

Normal prostate examination
17 patients
No correlation with PSA
Normal PSA 2/2 (+)
Abnormal PSA 14/15 (+) 1/15 (-)
No correlation with ultrasound
Hypoechoic 67% (+)
Isoechoic 65% (+)

Table 4

Stanford post external beam radiation therapy biopsies J Urology, August, 1989

Questions

Confirmation of pathologic observations?

What is the total group from which the 15 (+) are selected?

*2-10 years after ebrt
~100 per year ~800 treated
Less dead, ID, LR ~400
Alive without ~400

A new biology for Gleason 8, 9, 10 cancer?

*5 patients 2-9 years after
RX with Gleason 8, 9, or 10 cancer
and normal prostate exam

treated in 1973 and 1978 (16), the RTOG data are from prospective trials between 1978 and 1985 (17). There is still room for us to study means of improving local control, but essentially all stage T1 (stage A), 75% of T2 (stage B) and 60% of T3, 4 (stage C) patients will not express first failure in the prostate by 10 years.

Stamey's group has recently published on pathologically persistent cancer in a very small group of patients treated with external beam radiation therapy and without clinical abnormality in the prostate (18). Table 3 tabulates the data in clinically normal glands and Table 4 lists some of the questions that must be answered if we are to extrapolate his finding beyond the 17 patients submitted to biopsy, to the 400 or 500 other survivors. Perhaps the greatest difficulty is in believing that post-irradiation Gleason 8-10 cancer (5 of the 17) will lie dormant in the prostate for long periods of time—suggesting a new biology for poorly differentiated prostate cancer.

Ten-year USA national averages for external beam radiation therapy

Fig. 5 (A, B, C) shows the USA averages for survival after external beam radiation therapy (13). They are quite comparable to single institution series and illustrate that the technology of treatment is well disseminated in the USA as a whole. We have identified areas of poor treatment in the United States and are working on eliminating them (19, 20).

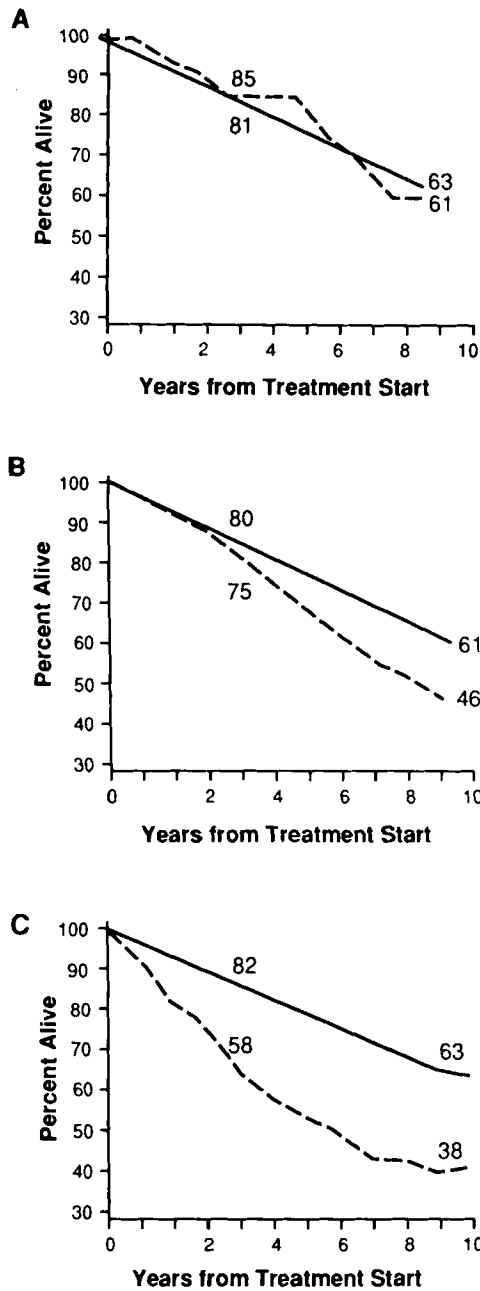


Fig. 5. US national averages for survival (treated 1973, 1974). A) Stage A patients; B) Stage B patients; C) Stage C patients. — Expected survival; - - - Observed survival. (Modified from Hanks Int J Rad Oncol Biol Phys 1985; 11: 1235-45.)

In the USA, T1 (stage A) patients match their expected survival, T2 (stage B) patients are within 16% of their expected survival at 10 years and T3, 4 (stage C) patients fall 26% below expected. Once again, this includes patients of all states of health and all histologic grades and is not selected as are all surgical series.

There is no evidence that the average urologist in the US performs the radical prostatectomy procedure, (in particular, the nerve-sparing variation) with comparable outcome

to the few centers of surgical expertise that report their results. This is a major concern for the patient.

Randomized trials

Randomized trials of alternatives of treatment have been conducted in Veterans Administration Hospital patients by the VACURG group and the uro-oncology groups (20-22). A summary of 6 of these trials is given in Table 5. These trials have several common drawbacks which are poor compliance, few patients, an excessive time for accumulation of patients into the studies and results that are not consistent as a result of these studies having not been well accepted by critical observers.

Five and ten-year data in node-negative patients treated with radiation or surgery

The uro-oncology trial of radical prostatectomy versus external beam radiation therapy is a seriously flawed study, and some of the problems are given in Table 6 (23). Fig. 6 compares the uro-oncology trial of lymph node dissection negative clinical T1b (A2) and T2 (B) patients with prostatectomy or radiation with the same uro-oncology group trial of lymph node-negative T3 cancers treated with radiation or delayed hormone manipulation (24, 25). The rate of failure observed in the T1b2 (stage A2 and B) patients treated with radiation was exactly the same as that observed after treatment of T3 (stage C) patients with radiation. The conclusion is inescapable that the randomized trial of radical prostatectomy versus external beam allocated patients with the outcome of T3,4 (stage C) patients to irradiation and that of T1b2 (stage A and B) patients to surgery.

Our 1973 national survey included 65 patients with

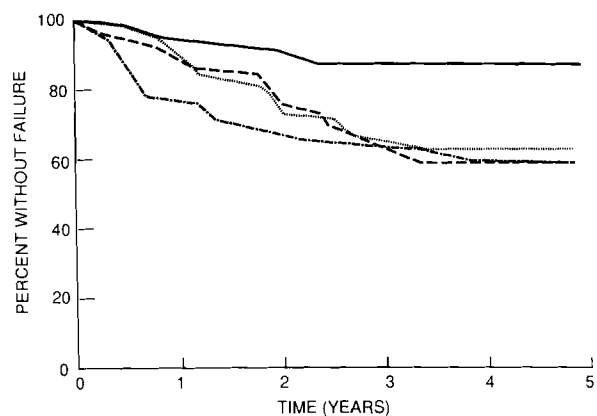


Fig. 6. Comparison of uro-oncology studies in stages A and B and stage C patients. Veterans Administration Hospital. — Prostatectomy, stage A and stage B; - - - Radiotherapy, stage A and stage B; - . - . - Delayed androgen deprivation, stage C; Extended field irradiation, stage C. (Modified from Hanks Suppl. to Urol 1989; 23: 21-6.)

Table 5
Prospective trials in Veterans Administration hospital patients

Group	Stage	Question	Result
1. Vacurg	A1, A2, B	Prostatectomy vs placebo	No differences
2. Vacurg	A1, A2	Placebo/estrogen/ orch + plac/orch + estr	No differences
3. Vacurg	A1, A2	Prostatectomy vs # 2	No differences
4. Uro-oncology*	A2, B	Prostatectomy vs radiation	Prostatectomy superior
5. Uro-oncology*	T3, N0	Radiation vs delayed horm	No differences
6. Uro-oncology*	N(+)	Radiation vs delayed horm	Radiation superior

*These trials are internally inconsistent.

Table 6

Problems of the study, analysis and reporting of the uro-oncology research group comparison

- Many lost or dead of intercurrent disease (56% in 4-7 years)
- Incontinence rate of 12%-40%
- Radiation therapy committee not involved in data analysis
- Suggestions of radiation therapy committee ignored
- Inappropriate end point
- Questionable method of randomization
- Assigned treatment received by 90 of 106 (85%)
- Radiation therapy received by 4 of 47 assigned surgery
- Surgery received by 3 of 59 assigned radiation
- Positive surgical margins eliminated (2 patients)

LND negative A2 and B cancer. Their failure patterns are shown on Table 7 and are markedly different from the result of the uro-oncology group (24). We have also reported with others the failure patterns of four groups of patients who were LND negative stage A and B treated with external beam radiation therapy (Fig. 7). None of these groups of patients showed anything near the failure observed in the Paulson uro-oncology study (26). They include more than 200 patients in contrast to 52 in the uro-oncology study.

We have recently updated the follow-up on the 104 RTOG patients who were clinical stage A2 and B and treated with external beam radiation (Fig. 8) (Hanks et al., Unpublished study). Their survival exceeded the expected for the full 10 years of observation and the absolute failures observed were 9 local, 3 local plus metastasis and 11 metastasis alone. The survival of these patients equals or exceeds any comparable surgical series (27).

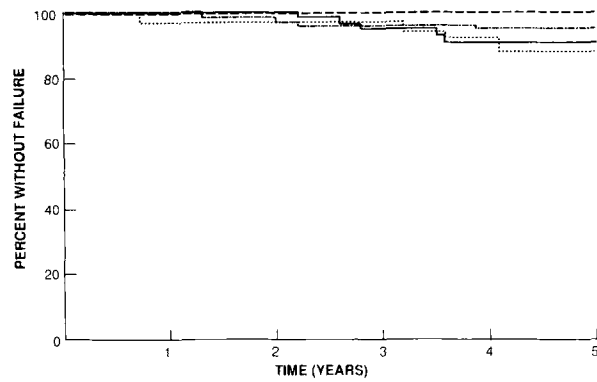


Fig. 7. Any failure analysis for node-negative stage A2, B patients. (Modified from Hanks Suppl. to Urol 1989; 23: 21-6.) — Stanford (n = 51); - - - Mallinckrodt (n = 140); - · - · - RTOG (n = 104); · · · · PCS (n = 37).

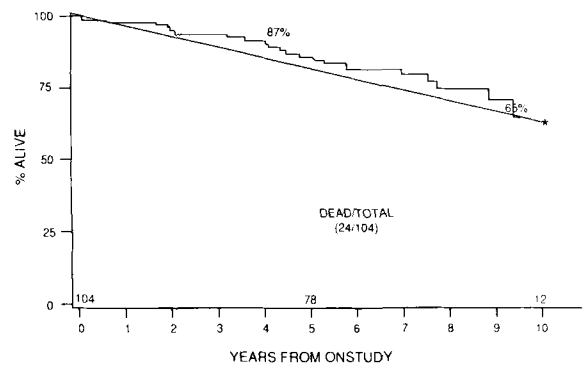


Fig. 8. Survival of node-negative stage A2, B patients after radiation therapy RTOG 7706. Patients with laparotomy and normal SAP. * = age-matched expected survival.

Table 7

Results of 65 patients with stages A and B after negative lymph node dissection

Treatment group	Stage		Failure			Total failure	
	A	B	Isolated infield	Infield & metastases	Metastases	No.	Percent
EBXRT	10	27	1	1	3	5	14
I-125 implant	5	23	0	3	1	4	14

Table 8*Multi-institutional trials in prostate cancer RTOG/SWOG*

Radical prostatectomy vs radiation (A2, B, N0)
Adjuvant irradiation for pathologic stage C
Radiotherapy vs radiotherapy + zolodex (B2, C)
Radiotherapy vs cytoreduction with flutamide and zolodex + radiotherapy (B2, C)
Post irradiation biopsies—all new studies

Important ongoing or planned clinical trials

Several important questions about the management of prostate cancer are or will be subjected to prospective trial by RTOG or SWOG. These are listed in Table 8. Only through large carefully controlled, carefully executed and reported, multi-institutional trials will we know the answer to many of our questions about the care of patients with prostate cancer.

Radiation therapy in stage C cancer

Radiation therapy is the only useful curative treatment of T3,4 (stage C) cancer. Long-term results in 1 800 patients from 3 single institutions and from the PCS national surveys are shown in Table 9 (10, 11, 26). The results of treatment of this stage of prostate cancer is open to improvement by testing new strategies in prospective trials, but until those are complete external beam radiation therapy provides local control of the cancer, long-term disease-free survival and hope for many.

Table 10*Preservation of potency*

Author (ref. No.)	n	Percentage potent	Modality
Walsh et al. (28)	250	72	Surgery
Catalona et al. (7)	250	58	Surgery
Bagshaw et al. (10)	434	86	Radiotherapy
Hanks (24)	100	47-73	Radiotherapy

Sequellae of radiation

Sequellae of radiation therapy are extensively reported and well-documented. Our USA national averages are known from the study of 1 400 treated patients and are modest and rarely severe (24). These studies show that about 5-6% of treated patients will require admission to the hospital for diagnosis or treatment of a radiation sequellae. This includes the 2% who will require surgical intervention ranging from cystoscopic relief of bladder neck stricture to repair of bowel injury. There was only one death due to sequellae in 1 400 patients (24).

Potency is preserved in most patients after external beam radiation with 70-85% of patients potent 1-1 1/2 years after treatment (10, 24). Preservation of potency after surgery is stage-related and varies with the surgical series stage content. The range is 58% overall to 72% overall (7, 8) (Table 10).

Conclusions

Clinical observation of thousands of patients treated with external beam radiation over the last 30 years demonstrate

Table 9*Prostate cancer, stage C (T3 or T4)*

Center	No.	5 yr		10 yr		15 yr	
		S	FFR	S	FFR	S	FFR
Stanford							
T3	348	64%	46%	35%	28%	18%	23%
T4	32	27%	17%	12%	17%	-	-
MD anderson			DFS		DFS		DFS
stage C	551	72%	59%	47%	45%	27%	40%
Wash Univ			NED		NED		
	328	65%	53%	35%	32%		
			NEDS		NEDS		
US national averages							
1973	296	58%	39%	38%	28%		
1978	237	65%	50%				

S = survival, FFR = freedom from relapse, DFS = disease free survival, NED = no evidence of disease, NEDS = no evidence of disease survival.

long-term local control and long-term survival free of disease for many patients with prostate cancer. This modality is available to patients of all states of health and should be the only curative treatment consideration for stage T2b (stage B2), T3, 4 (stage C) and poorly differentiated cancers of any stage.

Modern surgical support and modification of the radical prostatectomy procedure has begun to develop 5–10-year data that suggest surgery to be equivalent to radiation for the patient with low-volume T2a (stage B1) low-grade prostate cancer. There is no evidence that surgical results at 10, 15 or 20 years after treatment of T2b (B2) prostate cancer approach those obtained with radiation in comparable patients, and there are abundant pathologic data that T2b (stage B2) patients have locally extensive cancers that are not susceptible to surgical cure.

The few old randomized trials have been poorly conducted and do not contribute to a comparison of treatment methods.

New trials beginning in RTOG, SWOG and ECOG may provide some believable answers to pertinent questions in 10–15 years.

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