NEUTRON RADIATION THERAPY WITH THE HARPER HOSPITAL SUPERCONDUCTING CYCLOTRON: SIX YEARS OPERATING EXPERIENCE

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The last three years has seen a significant increase in the number of patients treated with neutron therapy at the Gershenson Radiation Oncology Center. In the sixth year of operation (March 1997 - February 1998) 223 patients were treated with 9085 fields in 2198 fractions, an approximately 25% increase in the number of fields compared with the previous year. In spite of the increased patient load the cyclotron has maintained a five day (50-55hour/week) clinical schedule with 6.8% downtime. The relatively high number of fields per fraction (4.1) reflects the fact that most patients are treated with complex conformal irradiation techniques. Approximately 75-80% of the patients treated to date have been prostate cancer cases. Our results in this group of patients lead us to conclude that mixed neutron/photon irradiation is the radiation treatment of choice for these patients. Furthermore such treatment can be shown to be cost effective in comparison with conventional x ray therapy. Details of accelerator performance and strategies for further improving efficiency which will result in greater cost effectiveness are discussed.

1. Introduction

The Harper Hospital/Wayne State University Fast Neutron Therapy Facility has been treating patients on a full-time basis since March of 1992. The facility uses a unique superconducting cyclotron which was designed and built at the National Superconducting Cyclotron Laboratory, Michigan State University by Dr. Henry Blosser and his colleagues. The design of the cyclotron and its use as source of neutrons for external beam radiation therapy are described elsewhere [1,2,3]. The last three years have seen a significant increase in the number of patients treated with neutron radiation therapy at this center. In the sixth year of operation (March 1997 thru' February 1998) 223 patients were treated with 9085 fields in 2198 fractions. During this year the facility was used for approximately 85% of the scheduled treatment time and in spite of the increased load and high ultilization the downtime remained at a level of less than 7%. Statistics on the patient load and cyclotron downtime are given.

Of the 223 patients treated in 1997-98 there were 191 cases of adenocarcinoma of the prostate (85.6%). Each of these patients was treated with a total of six irradiation fields; most were treated with three neutron fields per day alternating the fields treated each day. Some patients, however, are treated with six fields per day; these are the larger patients in which skin sparing effects must be maximized. The net result of this is that the average number of treatment fields per patient is approximately four. This relatively high number is a reflection of the fact that most of our neutron patients, and all of the prostate patients, receive conformal radiation therapy which involves state-of-the-art three-dimensional treatment planning. techniques. The emphasis of our neutron therapy program on the treatment of adenocarcinoma of the prostate has lead us to perform a detailed cost effectiveness analysis of neutron therapy in comparison to conventional photon therapy. The results of this analysis show that, contrary to popular belief among the radiation therapy community, neutron therapy can be a cost-effective modality in the treatment of prostate cancer [4]. These results are reviewed briefly and strategies for both increasing the patient throughput and decreasing downtime are discussed, which can lead to further improvements in cost-effectiveness.

2. Patient Load

Since the inception of a full-time neutron therapy program at Harper Hospital in March 1992, a total of 929 patients have been treated with neutron therapy (up to May 31, 1998). Table 1 shows how these patients are distributed among the various disease sites. The table clearly shows that prostate cancer cases predominate (77.28%). Head and neck tumors (mainly adenoid cystic histology), sarcoma, lung and parotid account for a further 16.68% of the cases. This is hardly surprising since prostate cancer, adenoid cystic tumors of the head and neck (including parotid glands), sarcomas and some lung tumors are those diseases that have been identified as good candidates for fast neutron radiation therapy. Although the number of disease sites for which neutron therapy is indicated is limited, there are

Table 1 : Patient treatment summary; March 1992 - May 1998.

Anatomical Site	Number of Patients	Percent of Total
Prostate	718	77.28
Head & Neck	51	5.49
Sarcoma	47	5.06
Lung	36	3.87
Parotid	21	2.26
Pancreas	10	1.08
Gynecologic	9	0.97
Rectum	6	0.64
Breast	5	0.54
Melanoma	5	0.54
Bone Metastases	4	0.43
Unknown	3	0.32
Thyroid	2	0.22
Brain	2	0.22
Kidney	2	0.22
Others Bladder, colon, bone, kidney mets., pelvic adenoca., ureter, histiocytoma, biliary duct. (One of each.)	8	0.86
Total	929	100.00

over 300,000 new cases of prostate cancer each year in the USA and this patient volume alone is enough to justify the extensive use of neutron therapy; particularly as fast neutron therapy has been shown to be superior to conventional therapy in two phase III clinical trails [5,6]. These results will be discussed in more detail latter.

3. Cyclotron Downtime

During the first year of clinical operation detailed records of cyclotron downtime were not kept; the patient load was very low at this time and most problems could be overcome without effecting the flow of patients. In the second year detailed record keeping was started and Table 2 is a summary of the major causes of cyclotron failure. The second item, listed as a water leak was due to failure of an internal RF water cooling pipe which had been damaged during the manufacture of the accelerator. This problem has not recurred. It is listed as a separate item because it was seen as an unusual occurrence.

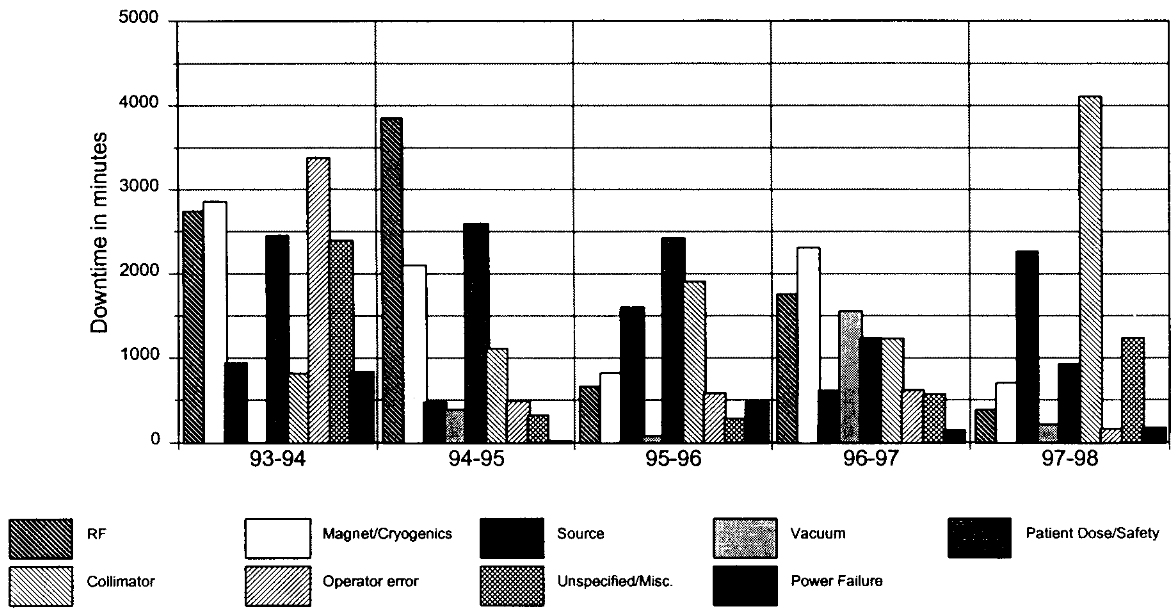
In fig. 1 this event has been excluded from the analysis and downtime is allocated to a limited number of facility sub-systems or categories including: magnet/cryogenic system, RF system, ion source, vacuum system, patient dose delivery and safety system, operator error, unspecified/miscellaneous and power failure. In this figure data are presented for each year for which records are available. A prominent feature of this graph is the noticeable drop in operator errors after the first year. It is also clear that the vacuum system gives little trouble but that all the other major systems have been the cause of considerable downtime at some time. The patient dose monitoring and safety system is the only system which shows a systematic improvement over the years. The beam collimator which was troublesome during the first year of record keeping showed considerable improvement in its reliability up to last year when it was the single largest source of downtime. This correlates with "wear and tear" as the parts in this pneumatic-electro-mechanical device fail after repeated use. A major rebuild of the collimator is scheduled this year.

Table 2: Cyclotron downtime analysis; March 1993 - May 1998.

Cause/Problem	Percent of Downtime	Hours
Water leak (internal RF cooling line)	14.46	172.8
RF System	13.77	164.2
Collimator	13.39	159.9
Magnet /Cryogenics	12.42	148.2
Operator Error	9.79	117.0
Ion Source	9.55	114.0
Unspecified	6.19	74.0
Console	4.67	55.8
Vacuum System	3.37	40.3
Hydraulic Door	2.50	29.9
Power Failure	2.38	28.4
X ray Set	1.87	22.4
Gantry	1.80	21.5
Treatment Couch	1.49	17.9
Miscellaneous (<1% per time)	2.35	28.1
Total	100.00	1194.7

It should be noted that patient treatments may be scheduled on the superconducting cyclotron for 10 hours each day and for 52 weeks of the year (with only 6 days of national holidays). All routine and preventive maintenance is carried out in the evenings and on weekends. Anytime between 7:00 a.m. and 5:00 p.m. when the cyclotron is not available as a

Figure 1. Yearly summary of cyclotron downtime since records began in 1993-1994 operating year. Downtime is listed by major sub-system or category.



result of cyclotron or ancillary equipment failure is logged as downtime.

4. The Treatment Prostate Cancer with External Beam Fast Neutron Therapy at WSU.

Since 1992 over 700 patients with prostate cancer have been treated with fast neutron therapy at WSU. The treatment technique has developed over the years and most patients are now treated with a six field technique in which 10-11 Gy of neutrons are delivered over 10 or 11 days with prior or subsequent treatment with 40 Gy of photons in 20 fractions. Our studies show that the RBE of neutrons is about 4 [7], so that patients are receiving at least 80-84 equivalent photon Gy. The WSU experience has been reviewed recently by Forman *et al* {8]. Many patients have been entered on phase I or II institutional trials, and although no phase III trial against conventional x ray therapy has been undertaken, the WSU results show that the outcome of neutron therapy, as measured by biochemical absence of disease, are as good as or superior to the best results obtained at WSU with the most sophisticated conformal photon treatment. In patients treated with 10-11 Gy of neutrons at WSU complications of ≥grade 3 occur in only 2-3% of the patients.

5. Cost Effectiveness Analysis.

A detailed cost effectiveness analysis has been made which compares mixed neutron/photon therapy as delivered at WSU, with conformal photon therapy combined with neo-adjuvant hormonal therapy [4]. This latter therapy may be regarded as the present standard of care in the USA. In oncology a cost effectiveness study is comprised of two parts. Firstly, a demonstration of the clinical effectiveness of the two modalities showing that the outcome of one is superior or comparable to the other, for the same level of treatment related complications. Secondly, a cost analysis showing the relative cost of delivering a full course of each of the competing therapies.

5.1 Clinical Effectiveness

There have been two phase III clinical trials of neutron therapy in the treatment of prostate cancer funded by the National Cancer Institute (NCI) in the USA. The earlier of these two trials compared mixed beam photon/ neutron treatment with conventional x-ray therapy and found that both 10 year local disease control and survival were superior to conventional therapy; with comparable complication rates in each group of patients [5]. The later trial compared neutrons only with conventional x ray therapy [6]. Five year results showed improved local control and better biochemical disease control as measured by PSA levels. However, complications were much higher in the neutron arm. Patients were accrued to this trial from 3 main centers UCLA, M.D.Anderson Hospital (MDAH) and the University of Washington (UW) in Seattle. The complication rates observed at these three institutions were vastly different and the severity and degree of complications correlated well with the sophistication of the neutron collimation techniques used at each institution.MDAH used a limited selection of rectangular inserts, UCLA a continuously variable jaw collimator capable of producing

Table 3. Results of studies in prostate cancer using neutrons alone, mixed photons/neutrons and photons combined with hormones.

Endpoint	Neutrons + Photons Phase III	Neutrons Alone Phase III	Photons + Hormone Phase III
5 yr local control	93%	89%	54%
5 yr survival	62%	73%	58%
5 yr bNED PSA <4ng/ml		83%	36%
Complications ≥ Grade 3 or severe	9%	39% (UW 10%)	7.4%

square and rectangular fields, and UW used a multileaf collimator which produced irregularly shaped fields. The combined complication rates at MDAH and UCLA compared to those at UW (for ≥ Grade 3 complications) were 10% vs 45%, respectively.

The results of a phase III trial to investigate the effectiveness of conformal photon therapy combined with neo-adjuvant hormonal therapy in comparison to photon only therapy have been published by the Radiation Therapy Oncology Group in the USA [9]. The results of this trial and the two neutron trials are summarized in Table 3.

5.2 Cost analysis.

A cost analysis has been performed based on the 1996 Harper Hospital budget for the Gershenson Radiation Oncology Center and using the neutron therapy treatment data for the calender year 1996. One hundred and eighty one patients were treated with neutron therapy that year. The analysis compares 10 Gy of neutrons in 10 fractions + 40 Gy of photons in 20 fractions with 70 Gy of photons in 35 fractions + hormonal therapy. Based on these figures, treatment fraction specific costs were identified and the cost of delivering a single fraction of neutron therapy was found to be $532 compared to only $53 for a photon fraction. The photon figure assumes full capacity usage of the linac whereas as the neutron figure is based on the actual 1996 utilization data. When these costs are combined with other non-fraction specific costs the total cost of a course of conventional photon therapy is $18871, while a course of mixed beam photon/neutron therapy cost $20142 at WSU in 1996. Details of this analysis are published elsewhere [4].

6. Future Plans and Conclusions

The Harper Hospital superconducting cyclotron continues to operate satisfactorily in the clinical environment with acceptable downtime (~7%). The facility at WSU/Harper can claim to be the busiest neutron radiation therapy center in the world. We have demonstrated that the costs of neutron therapy for treating prostate cancer are comparable to those of the generally accepted conventional photon radiation therapy alternative. We are considering ways in which we can further improve cost effectiveness; these include increasing the working day to 14 hours and replacing the multirod collimator with a computer controlled multileaf collimator. Increasing the working day would be greatly helped by the development of a continuous flow cryogenic system to replace the batch fill method presently used as discussed in the proceedings of the previous cyclotron conference [10]. Manpower shortages due to hospital budget cuts have delayed this project. The multileaf collimator would allow field changes to be made without the radiation therapist (radiographer) having to enter the treatment room. We estimate that with these changes we could double our throughput to 450 patients per year. With this load the cost of a course of mixed beam photon/neutron therapy would be reduced to $18,532. Since, much of the high cost of neutron therapy is associated with high capital costs, one strategy for reducing the cost per treatment is to biuld large centers with a single cyclotron and multiple gantries. This approach is at present being applied in developing proton therapy facilities; a similar approach would be appropriate for neutron therapy centers specializing mainly in the treatment of prostate cancer.

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