

Original Research Article

A study of the effect of pre-radiation on healing of surgical wounds in the treatment of cancers of the head and neck

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ABSTRACT

Background: Radiation therapy is an established modality in the treatment of head and neck cancer patients. It is used alone or in combination with surgery and chemotherapy. Although radiotherapy is useful to affect tumour death, it also exerts a deleterious effect on surrounding normal tissues. These effects are either acute or can manifest months or years after the treatment. The chronic wounds are a result of impaired wound healing. Compromised wound healing in irradiated tissues is a common and challenging clinical problem.

Methods: A prospective observational study was done in a tertiary care teaching institute, Kolkata. The effect of radiation on surgery of cancers of head and neck was studied in 50 patients. The patients were divided into 2 groups of 25 each. The cases in the first group were irradiated prior to surgery and those on the second group were operated upon without any pre-radiation.

Results: The highest incidence of wound complications in those patients who were operated upon within 2 weeks to 6 months of completion of RT (83.33%). Patients who had their blood Hb level at or above 11 gm% developed less number of wound complications (34.78%) as compared to those who had their blood Hb level between 8-11 gm% where complication rate was 48.15%. Those patients who had their oral cavity or pharynx opened during surgery had a much higher incidence of wound complications (54.54%) than whose oral cavity or pharynx were not interfered with (17.64%). Wound infection was 36% in the irradiated group and 12% in the non-irradiated group. Separation of wound edges or skin necrosis followed in 28% cases in the pre-irradiated group and in 8% cases in the non-pre-irradiated group.

Conclusions: Radiotherapy is an integral modality of head and neck cancer therapy. Compromised wound healing is an important side effect of radiation therapy. All sorts of local complications as wound infection and necrosis, or ocutaneous fistulae, carotid artery perforation etc. are more pronounced in patients, who received prior radiotherapy. The complication of surgery after radiotherapy was found to be more pronounced between 2 weeks to 6 months in this series.

Keywords: Complications, Effect of radiation, Head and neck cancers, Radiation therapy, Wounds healing

INTRODUCTION

Modern multimodal treatment for cancer which comprise principally of surgery with radiation and chemotherapy

has improved the prospect of quality and quantity of life for the unfortunate patients suffering from head and neck cancer. The combined use of radiation and surgery has been practiced for a considerable time period and of late

they are used quite frequently in different protocols. One of the integral components of this treatment is the use of ionising radiation to effect tumour death. Such ionizing radiation though required for tumour death, also causes damage to the surrounding normal tissue.^{1,2}

There have been tremendous refinement and improvement both in the fields of surgery and radiotherapy. In spite of refinements radiation leaves behind noticeable and unnoticeable damage to the tissue. Radiation retards the tissue healing is known for many decades- since its use standard in cancer therapy.³ Of late groups of workers are coming out with reports that pre-radiation does not significantly retard the healing of surgical wounds.

Surgeons, especially of this country, frequently face with wound disruption, necrosis, or cutaneous fistulae following surgery in pre-irradiated head and neck cancer patients. Complications after radiation therapy occur in up to 60 percent of surgical patients. Clinical sequelae include skin atrophy, soft tissue fibrosis, desquamation, epithelial ulceration, fistula formation and major vessel rupture.^{4,6} Impaired peri and postoperative wound healing and the complications associated with it can be observed frequently.^{7,8} Things have now changed for the better undoubtedly but the problems have not disappeared completely. The present study is a modest endeavor to find an answer to these controversial reports.

METHODS

This prospective observational study was done in a tertiary care teaching institute, Kolkata, West Bengal. Institutional ethics committee permission was taken before starting enrolling patients for the study. Individual written informed consent was taken from each study before enrolling for the study. The effect of radiation on surgery of cancers of head and neck was studied in 50 patients. The patients were divided into 2 groups of 25 each. The cases in the first group were irradiated prior to surgery and those on the second group were operated upon without any pre-radiation.

The cases were evaluated by a board of experts and the board determined the course of action to be taken i.e. radiotherapy, chemotherapy, chemotherapy followed by surgery, radiotherapy followed by surgery or surgery only. The patients in either group i.e. those who underwent post-radiation surgery and those who underwent straight forward surgery were subjected to the same investigations and examinations as preparatory procedure. The cases were studied on basis of the following:

- Age group of the patient
- Sex
- Pre-operative findings of the lesion as per clinical examination

- Type of radiotherapy machine used and the dose given
- Time gap between the date of completion of radiotherapy and surgery
- Pre-operative blood Hb% of the patient
- Operative factors i.e. whether oral cavity or pharynx opened or not
- Type of complications
- Primary healing took place or not
- Total stay in hospital

The name, age, sex, initial finding, type of radiotherapy machine used and the dose, time gap between completion of RT and surgery etc. were all studied from hospital case records. The pre-operative blood Hb level, operative factors i.e. whether surgery involves oral cavity or pharynx, rate and type of complications, rate of primary healing, and total stay in hospital of the patient were all studied in the present work.

Regarding radiotherapy it is to be noted that following opinion of the board of experts, the patients were subjected to radiation and their progress closely followed every week. Those cases who were not responding at all were subjected to surgery long before the full course of RT was completed.

Those who did respond were subjected to surgery after a variable interval of time for the residual lesion. There was another group who was operated upon for recurrence after RT. The recurrences in 3 cases were away from the primary sites. There were two cases who underwent surgery for complication of radiotherapy i.e. osteonecrosis of mandible. The RT machine used in this series was a conventional one. In 3 of the cases the full curative dose of 6000 rads were not given due to non-responsive growth and the cases were subjected to surgery. The rest of the cases were given the full curative dose of 5000 to 6000 rads.

The patients who were selected for surgery were judged carefully according to their general condition i.e. the patients who were otherwise fit were taken up. The following investigations were routinely done:

- Examinations of blood for TLC, DLC, Hb%, bleeding and clotting time, serum creatinine, urea and sugar (fasting and post-prandial)
- Urine and stool for routine examination
- X-ray chest (PA view)
- X-ray of the affected part
- ECG

Care was taken to include those cases for whom the above investigations were within normal limits. During the post-operative period the patients were routinely given amoxicillin 500 mg 8 hourly till 8th post-operative day. For those patients whose oral cavity or pharynx were opened metronidazole was given in addition, initially 500

mg 8 hourly by intravenous route and later orally 400 mg 8 hourly for 7 days. The drains were removed on the third or 4th post-operative day and stitches on the 8th or 10th day. When wound infection was suspected a swab culture was taken and the appropriate antibiotic instituted according to the sensitivity test report. In addition regular dressing with povidine iodine solution was done and sometimes an ointment of the same substance was used till the wound healed or further repair was undertaken.

In the 12 cases developing wound infection 5 needed a secondary suture or skin grafting- the rest being cured by the above procedure. Total six cases developed or cutaneous fistula. In the non-irradiated group – one fistula was very small and healed spontaneously with dressing alone. The others were treated with a local rotation flap. In all the cases the pedicles were detached after 3-4 weeks and the patients discharged.

RESULTS

This study consisted of 50 patients in 2 groups- group A and group B. In group A the patients received irradiation prior to surgery and were operated upon for residual growth, recurrence of growth or merely a salvage procedure. In group B the patients were controls and received no pre-operative radiation.

Table 1: Percentage of cases developing wound complications.

Group A (pre-radiated group)	Group B (non-pre-radiated group)
14 (56%)	7 (28%)

Table 2: Types of wound complications in the irradiated group and in the non-irradiated group.

Types of wound complications	No. of patients	Percentage
Irradiated group (25 cases)		
Wound infection	9	36
Separation of wound edges	7	28
Orocutaneous fistula	4	16
Perforation of carotid artery	1	4
Death	2	8
Non-irradiated group (25 cases)		
Wound infection	3	12
Separation of wound edges	2	8
Orocutaneous fistula	2	8
Perforation of carotid artery	0	0
Death	1	4

The patients were selected consecutively according to hospital admission. Alternative cases of groups A and B were taken up for the present study.

No other criteria for selection were made. The age groups of the patients were between 31 to 80 years. Patients

below or above this group were not taken as they were not available. Total 13 patients were female and 37 male in this study. Approximately 14 (56%) patients in group A developed some sort of wound complications, whereas 7 (28%) patients in group B developed wound complications (Table 1). It shows that the percentage of cases developing wound complications is considerably higher in the irradiated group.

Table 3: Primary healing of wounds.

	No. of cases	No. of primary healing	Percentage
Pre-irradiated	25	11	44
Non-pre-radiated	25	18	72

Table 4: Incidence of wound complications in relation to sex.

Group A	Group B
Male 11/20(55%) [complications]	5/17 (29.41%)
Female 3/5 (60%) [complications]	2/8 (25%)

From the above table it is to be noted that the percentage of complications of all types are considerably higher in the pre-radiated group (Table 2). One patient died in the irradiated group post-operatively from a massive myocardial infarction and the other died from laryngeal oedema. In the non-irradiated group the only mortality was from a possible pulmonary embolism.

Table 5: Incidence of wound complications in relation to age.

Age in years	No. of cases	No. of complications	Percentage
31-40	4	0	0
41-50	19	8	42.10
51-60	21	9	41.86
61-70	5	3	60
71-80	1	1	100
Total	50	21	42

Table 6: Incidence of wound complications in relation to pre-operative hemoglobin level.

	No. of cases	No. of complications	Percentage
Cases below 11 gm% Hb	27	13	48.15
Cases at or above 11 gm% Hb	23	8	34.78

The number of cases who had primary healing of wound after operation was also higher in the non-pre-radiated group (Table 3). In group A 5 patients were female whereas in group B 8 cases were female.

It is to be noted here that in either group the complication rate is more or less the same for either sex and possibly does not play any role in wound healing (Table 4). The incidence of complications steadily rises with the

increase in age, and reached 100% in the 8th decade of life though there was only 1 case in that group who underwent surgery after irradiation. The overall complication rate was 42% (Table 5).

Table 7: Incidence of wound complications in relation to time gap between radiation and surgery.

Time Gap	No. of cases	No. of complications	Percentage
0-2 weeks	6	2	33.33
2 weeks – 6 months	12	10	83.33
6-12 months	4	2	50
Above 1 year	3	0	0
Total	25	14	56

A better blood Hb picture definitely increases the prospect of good wound healing.

It shows that the highest incidence of complications were in the 2nd group i.e. those who were operated upon within 2 weeks to 6 months of completion of radiotherapy (Table 7).

It can be seen that the stay in hospital was persistently higher in group A than in group B (Table 8). Most of the patients who had to stay more than 30 days in hospital underwent further surgery for the complications mostly in the form of reconstructive procedure.

Table 8: Stay in hospital after operation.

Stay in days	No. of patients in group A	No. of patients in group B
10-15	7	15
15-20	4	2
20-25	1	1
25-30	4	3
30-45	2	3
45-60	2	3
More than 60	5	0

Table 9: Incidence of wound complications in relation to preoperative macroscopic skin condition.

Condition of skin	No. of cases	No. of complications	Percentage
Change in color	23	13	52
Loss of elasticity	18	11	61.11
Fixity to deeper structures	15	11	73.33

It was found in this study that when macroscopically the skin appears fixed to deeper structures the incidence of wound complication rises. Only a change in color of the skin gives 52% wound complications (Table 9).

DISCUSSION

Radiation is employed as neoadjuvant, primary and adjuvant therapy for head and neck cancer. This study consisted of 50 patients of head and neck cancer of which 25 were irradiated prior to surgery and the rest 25 received no pre-irradiation. These patients were taken from surgery department of a tertiary care teaching hospital, Kolkata. The patients in the pre-irradiated group were operated upon for residual growth, recurrence of growth or salvage procedure. The time gap between the date of completion of radiotherapy and surgery varied

according to necessity and no fixed time interval was planned.

In this study 55% male patients developed wound complications in the pre-irradiated group, whereas in case of females it was 60%. In the non-pre-irradiated group the percentage of cases developing wound complications were 29.41% for males and 25% for females. The total percentage of cases developing wound complications in the pre-irradiated group (group A) was 56% and in the non-pre-irradiated group (group B) it was 28% (Table 1). Habel in his series of 463 patients also found a definite increase in healing time of the irradiated group.⁹

Marchetta, Sako and Maxwell found wound complications developing in 43% cases who had pre-irradiation and 22% cases who did not have pre-irradiation.¹⁰

The percentage of cases developing wound complications in the present study is higher both in the pre-irradiated and non-pre-irradiated groups. It may be that Marchetta et al had lower incidence because their cases were pre-selected.¹⁰ They took only those cases who required development of large tissue flaps or combined intra-oral and neck surgery.

Griffin et al treated patients with neutron irradiation and mixed beam.¹¹ They found an average complications rate of 54% for those who had surgery following radiation. This correlates with the present figure of 56%. However, they had no complications with the 12 patients who underwent surgery without prior irradiation. For surgery following neutron irradiation Griffin et al had 73% complication rate. The present study was conducted with a conventional machine and as such comparison in this respect is not possible though Griffin et al concluded that neutron irradiation is not superior in respect to tumor control and tissue side effect.¹¹ Marcial, Henley, Ydrach and Vallecillo reports a 21% complication rate after salvage surgery following radical irradiation, which is a very low figure compared to other workers and also the present series.¹² Their lower figure may be due to the fact that they used surgery only as a salvage procedure and no other indications were taken into account.

Marcial et al reported 54% surgical complication rate following RT and 48% complication rate following straight forward surgery.¹³ These figures vary considerably with that of the present study for those patients who had no pre-radiation. Marcial et al had a very high complication rate for that group i.e. 48% whereas the present series had a complication rate of only 28%.¹⁴ The number of cases in their study was quite high i.e. 229 against the present 25. But other investigators got figures similar to present study i.e. Habel, Marchetta et al, Griffin et al.⁹⁻¹¹ The explanation could be that Marcial et al¹⁰ choose the patients randomly without any prejudice and the patients received a fixed dose of radiation in a fixed span of time i.e. 5000 rads in 5 weeks. They did not mention the time gap between radiation and surgery. The patients in the present study received variable doses of radiation and the time gap between radiation and surgery also varied.

In the age groups of 41-50 years, 51-60 years, and 61-70 years, the rates of wound complications were 42.10%, 41.86%, and 60% respectively. Finally in the age group of 71-80 years the complication rate rose to 100%. It is quite evident from these figures that with the advancement of age the rate of wound complications also rises. Advanced age signifies advanced state of atherosclerosis of blood vessels with resultant lesser supply of blood to the healing tissue. This intensifies the retarded healing process caused by radiation. As a result the wound is reluctant to heal in this advanced age group.

Griffin et al commenting on the age of patients states that age of the patient had no influence on complication rate

in their series.¹¹ This does not corroborate at all with the present figures and inference. The reason may be the smaller number of cases in the present series and that they concentrated more on the different types of radiation and their effect on wound healing than on the age group of patients and any way the exact figures regarding age group are also lacking in their paper.

Wound infection occurred in 36% cases in the irradiated group and in 12% cases in the non-irradiated group. Marchetta, Sako and Maxwell in their series found 24% cases of wound infection in the irradiated group which is lower than the present figures.¹⁰ In the non-irradiated group their figure of 11% corroborates with the present one. Separation of wound edges or skin necrosis followed in 28% cases in the pre-irradiated group and in 8% cases in the non-pre-irradiated group in the present series. Marchial, Henley, Ydrach and Vallecillo found 6% pharyngocutaneous fistula formation which is very low again in the pre-irradiated group.¹²

Wound healing occurs in an ordered sequence of cellular interactions. Repetitive radiation injury disrupts this highly organized sequence of events, resulting in repetitive inflammatory responses and ongoing cellular regeneration.¹⁴ There is an important distinction to be made between the early and the late side-effects of radiation therapy: Early side effects include erythema, dry desquamation, hyperpigmentation and hair loss.¹⁵ Late effects include skin atrophy, dryness, telangiectasia, dyschromia, dyspigmentation, fibrosis, and ulcers.¹⁶

Joseph et al gives 73% fistula formation in the patients radiated in "unplanned" fashion and 23% in those radiated in "planned" fashion.¹⁷ In no-irradiated group it was only 8%. Marchetta, Sako and Maxwell gives a figure of 22% in the irradiated group and 9% in the non-irradiated group.¹⁰ The present figure 16% in the irradiated and 8% in the non-irradiated group is close with Marchetta, Sako and Maxwell but not very close, because 16% is a much lower figure than the 22% of Marchetta et al or the 23% of Joseph et al (in the "planned" fashion group).^{10,17}

The 73% (in "unplanned" fashion group) on the other hand is too high. Perforation of carotid artery occurred in 1% cases in the irradiated group and in 0% cases in the non-irradiated group. This is quite low compared to the figures of Marchetta et al i.e. 7% and 16% respectively in the irradiated and non-irradiated groups.¹⁰ This corroborates with the present figure of 1%. Marcial, Hanley, Ydrach et al also gives similar figure of 2% but Marchial et al gives 5% for the pre-irradiated group which is a bit high and 2% for the non-pre-irradiate group which is also on the higher side.¹²

It was seen that 48.15% (13/27) cases of patients whose preoperative Hb level was below 11 gm% developed wound complications. In the other group of patients the Hb level in blood was 11 gm% or above. About 34.78%

developed wound complications after surgery. It can be seen from these figures that the rate of wound complications increases with the decrease in blood Hb level. Adequate blood Hb level is essential for proper wound healing. The pre-irradiated tissue is already compromised in relation to blood supply. Further lack of oxygenation due to low blood Hb level reduces the tissue healing properties.

In this study, the 25 patients who received pre-operative radiation were divided into 4 groups in relation to the time elapsed between the last dose of radiation and that of surgery. In the first group, there were 6 cases who underwent surgery within 2 weeks of the date of completion of RT. About 33.33 % cases developed wound complications. In the 2nd group of 12 cases who underwent surgery between 2 weeks to 6 months after completion of RT. Approximately 83.33% cases developed wound complications.

In the 3rd group, the time gap was 6-12 months and of the 4 cases 50% developed complications. It shows that the highest incidence of complications were in the 2nd group i.e. those who were operated upon within 2 weeks to 6 months of completion of RT. Powers, Ogura and Palmer (1967)¹⁸ in their series found no optimal dose of radiation or time delay between radiation and surgery to permit complete and adequate wound healing with minimum delay. However in their study of animals it was noted that 15 days appeared to be an optimum. There was less adequate wound healing before or after this optimum period.

This tallies with the findings of the present series in the second group who had complication rate of 83.33%. Powers et al also are of the opinion that 15 days interval between the last dose of radiation and surgery is appropriate.¹⁹ Silverstone and Associates recommend an interval of 21 to 42 days.²⁰ Their contention is that for the most tissues 3 weeks interval after cancerocidal doses is minimal and 6 weeks is probably the optimum. In the present series the maximum numbers of complications were in those cases that had surgery within 2 weeks to 6 months after completion of RT. In the present series minimum numbers of complications were in those cases who had surgery after 1 year of completion of RT, which does not corroborate with the recommendation of Silverstone and Associates.²⁰

Ketcham et al also found distressing results after performing surgery on subjects within 24 hours of completion of RT in a single dose.²¹ Though none of the patients in the present series were irradiated upon in a single dose, yet a complication rate of 33.33% was found in the patients who had operation within 2 weeks of completion of RT corroborating the conclusions of Ketcham et al.

The patients whose oral cavity or pharynx were opened during surgery had a much higher incidence of

complications in the present series. There were 33 cases whose oral cavity or pharynx were opened and 18 had wound complications (54.54%) whereas of the rest 17 cases there were 3 complications (17.64%). Powers, Ogura and Palmer also found a higher incidence of complications where the wound penetrated from the pharyngeal wall through to the skin, than with neck dissection only or removal of para-nasal or laryngeal lesions.¹⁸

Duration of stay in hospital in this series showed that the patients who had pre-operative radiation had a much longer stay than those who had no pre-operative radiation. After 25 days 18 patients in the non-preoperative radiations group (Group B) were discharged against 12 in the pre-operative radiation group (Group A). After 45 days 24 patients in group B had gone home whereas only 18 patients were discharged in group A. Five patients in group A had to stay in hospitals for more than 2 months whereas none in the group B had to stay that long. It is quite evident that pre-operative radiation, besides producing all sorts of other complications, increases also the stay in hospital of a patient thus incurring additional financial loss to the patient and to the State.

CONCLUSION

In this study of the effect of radiation on healing of surgical wounds for cancers of head and neck, two groups of patients of 25 each were selected at random. The first groups of patients were irradiated prior to surgery while the other received no pre-radiation. The effect of surgery on the two groups were analyzed along the following criteria-

- It was seen from this study that the rate of wound complications rises with the advancement of age.
- The rate of wound complications is more or less the same for both sex and possibly sex does not play any significant role in wound healing.
- The highest incidence of wound complications in those patients who were operated upon within 2 weeks to 6 months of completion of RT (83.33%). The lowest incidence was in those who had surgery after 1 year of completion of RT (0%).
- Patients who had their blood Hb level at or above 11 gm% developed less number of wound complications (34.78%) as compared to those who had their blood Hb level between 8-11 gm% where complication rate was 48.15%.
- Those patients who had their oral cavity or pharynx opened during surgery had a much higher incidence of wound complications (54.54%) than whose oral cavity or pharynx were not interfered with (17.64%).
- Wound infection was 36% in the irradiated group and 12% in the non-irradiated group. Separation of wound edges or skin necrosis followed in 28% cases in the pre-irradiated group and in 8% cases in the non-pre-irradiated group.

- The rate of pharyngocutaneous fistula was double in the pre-irradiated group (16% in the irradiated and 8% in the non-irradiated group).
- Perforation of carotid artery occurred in 1% cases in irradiated group and in none in the non-irradiated group.
- In the present series primary healing took place in 44% cases in the pre-irradiated group and in 72% cases in the non-pre-irradiated group. The rate of primary healing was seen to be much higher in the non-irradiated group.
- The total stay in hospitals as seen in this series was much longer in those patients who had pre-operative irradiation. After 25 days of operation 18 patients in the non-pre-irradiated group were discharged while only 12 in the pre-operative radiation group could be sent home. After 45 days 24 patients who had no pre-radiation could go home whereas 18 patients could only be discharged from the other group. No patients in the non-irradiated group had to stay in hospital after 2 months, whereas 5 patients in the irradiated group were not in a condition to be discharged after this time.

The effect of tissue healing in this small series of only 50 cases of irradiated and non-irradiated patients who had surgery shows that patients with prior radiation react adversely in its tissue healing properties. The advanced age of the patients with its withering arterial tree have less chance of primary healing than the young patients in pre-irradiated cases.

The low Hb content of blood prevents tissue healing in both irradiated and non-irradiated cases – more so in the former. All sorts of local complications as wound infection and necrosis, orocutaneous fistulae, carotid artery perforation etc. are more pronounced in patients, who received prior radiotherapy. The stays in hospitals of these patients were also longer. The complication of surgery after radiotherapy was found to be more pronounced between 2 weeks to 6 months in this series.

As the number of cases are small due to the paucity of time this subject needs an extensive search to establish these facts, as some modern investigations are pointing to a conclusion that pre-radiation does not hamper tissue healing (Marchial et al, 1982) as contrary to others (Habel, 1965; Marchetta et al, 1967; and Marcial et al, 1980).

As surgery following radiation is quite rampant now it will need a huge series of cases with proper double blind randomized controlled study to come to a statistically valid conclusion. It leaves behind an old visit for newer re-investigation.

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