DISCUSSION
OVERALL PRIMARY TUMOUR CONTROL

The 2 yr and 5 yr PRFSs, for all the pts together, of 64.9% and 58.6% is better than that reported in the literature, including that reported from RCC itself previously. One reason for this is the fact that all pts were managed by one radiotherapist. The risk of LN recurrence being removed in many by excision of the involved LN could also have contributed to this, though the technique of censoring during survival analysis lessens this effect. Another reason could be that pts with severe bone involvement were not given radical radiotherapy. Yet another reason is that those pts who had not taken full prescribed doses (such as those who did not take the last two or three fractions, on or with out medical advice), or treated by other schedules (which are taken as equivalent, but may not be so) were not included.

The relation of various factors, empirical (classical) and radiobiological, to primary tumour control was analysed by "CC analysis", KM survival analysis and time to recurrence analysis. Ancillary analysis was done to see the inter-relationships of factors which influenced treatment results. This was done particularly for those considered as empirical and apparently devoid of scientific explanation for influencing treatment result. Attempts were made to relate them to certain new investigative modalities and give new, alternative explanations for their influence.

TREATMENT FACTORS

Radiotherapy Schedule and Fraction Size

The type of schedule had a major and significant impact on primary tumour control and appeared to be the most important prognostic factor. The difference would have been higher but for the fact that many pts in CF had concurrent CT, compared to the few in AF. This difference between the two schedules has not been reported earlier. The earlier reports from RCC had assumed them to be equivalent, but the present study clearly shows that it is not so. Unlike most western series, the present study only deals with cancers of the BGP complex in the oral cavity and hence it is meaningless to compare them with the present. Other than
from Manchester reports on this AF are not available. Similarly reports on the CF used in the present study are also not available. This is because the usual total doses for a 5 weeks regime is upward of 65 Gy.

It is not clear why the results are so different for the two schedules. It is unlikely to be an indirect effect of the type of tumours included, because it was present for all Tsize groups, albeit significant for T2 alone. The lack of significance in T1 and T3 is obviously due to the small numbers. The AF and CF differ in three aspects: fraction size, OTT and total dose. The fraction size of AF (3.5 Gy) is nearly 1.5 times that of the CF (2.4 Gy) and the planned OTT of the CF is nearly 1.75 times that of the AF. Hence either the higher fraction size or the lower OTT must have been the reason for the superior results of the AF compared to CF. Associated with the fraction size is the fact that the AWD in AF is 17.5 Gy whereas in the CF it is only 12.0 Gy. But it is unlikely that the AWD per se made the difference, because the present results with the AF are better than that reported for CHART (REF) with an AWD of 22.5 Gy. The OTT of CHART was also lower, just 12 days. This suggests that, most likely, it is the fraction size alone that is responsible. Unlike the late reacting tissues, fraction size is not considered as important in tumour cell kill by radiation, presumably because $\beta$ kill is very low or near zero and the $\alpha/\beta$ ratio is consequently very high. The results of the present study suggests that fraction size is important in cancer radiotherapy too.

With in each schedule, the small alteration in fraction size used in a few pts does not seem to have influenced the treatment result apparently. This may be because of the small difference in fraction size or the small number of pts treated by the lower fraction size. Even if larger number of pts were available it is unlikely that effect of fraction size can be identified. The reason is that alteration in the fraction size occurred because the number of fractions had been increased by one in these pts and this leads to a reduction in AWD and also prolongation of OTT by not one day but as much as 3 days even if treatment is according to schedule.

**Concurrent BLM**

BLM is probably the most useful drug for concurrent use with RT in oral cancers. The findings of the present study also emphasizes this. When all pts are considered together, the addition of BLM did not seem to influence treatment results with radiotherapy. But situation was different when the two RT schedules were analysed separately. In the case of CF the association of BLM with primary tumour control was highly significant, collectively and for T1 and T2 tumours when considered together. But in T3 tumours even though the OR was 2.6
the association was lacking significance. This is probably due to confounding with other factors, very likely the various time related factors, as discussed later on. With AF there was no significant association between addition of BLM and local control. This could be because of three reasons: i.) BLM improves results with AF too and the lack of significance can be ascribed to the small number of pts who received the drug. This suggested by the fact that none of the pts who received BLM recurred, ii). The primary tumour control with the AF is so excellent that addition of CT is really not needed. In the BLM- group, proportion with recurrence was only 19.8%; iii.) There is confounding by other factors such as Tsize, time related factors, etc. Very likely all are operative. It is likely that the addition of BLM does improve local control with AF. The findings of the present study suggests that BLM does have synergistic activity with radiation and its addition may help overcome to some extent the shortcomings of an RT schedule.

OTT and OTT-extra days

The mean OTT in the controlled group was significantly lower than in the recurred group. In spite of the highly significant p value (0.000004) it is very difficult to interpret the meaning of this correctly. It may mean that OTT is really having an effect independent of the schedule or it may be reflecting the fact that more of those treated with AF (where the planned OTT is just 19 days) achieved primary control than those who had treatment with CF (where planned OTT is 33 days). The second is more likely because there was no significant difference in OTT in each schedule and in subgroups within each. If the influence of OTT is not independent of the schedule, then it may be invalid to use it as a factor when analyzing groups of patients treated by different schedules. This is because the time factor may not be the culprit; it may only reflect the overall inadequacy of the schedule or the prescription habit. In such instances, selecting the number of extra-days taken to complete the treatment over and above the planned OTT (the OTT-extra days) as a factor may be a better method to analyze the influence of OTT. When this was done it was seen that the difference between the controls and the cases was only nearly significant, the mean prolongation in the uncontrolled group being 0.9 days greater than that in the controlled group. With in each schedule even this was lacking, though in the CF group the mean prolongation was one day more in the cases than in the controls, suggesting that OTT could be important for the CF. But this one day prolongation does not truly reflect effect of OTT, but rather the effect of initial CIFI. Lack of influence of OTT does not mean that treatment time is not important. One reason for the overall lack of influence of OTT could be that the influence of OTT may be different, even opposite to each other, for tumours with different proliferation characteristics. An intense short duration regime may be required for rapidly proliferating tumours but may be unsuitable for slow growing tumours, where as a protracted regime, ineffective against rapidly growing
tumours, may be better suited than a short duration regime for slow growing tumours. In both
schedules, in the case of larger tumours, the mean OTT was greater for those which
developed recurrence, suggesting that larger tumours are more likely to be fast proliferating
and hence time is important for them. In the case of T2 tumours treated by CF, those which
were controlled had a higher mean OTT which may mean that T2 tumours, which are likely
to be slowly proliferating, may do better with a protracted OTT. A suggestion of the same
phenomenon is present in the findings in the relation of Tsize and clinical duration to tumour
control (vide infra). In the CF+BLM group too the controlled tumours had higher OTT, though
this could be the proxy effect of acute toxicity induced interruption. The results of the present
study thus suggest that OTT per se is not important in determining tumour control with RT and
the relation could even be in opposite directions for fast and slow growing tumours.

CIFl
In a 5 days/week schedule, the planned CIFl1_6 is 7 days. Analysis of CIFl1_6 showed that
prolongation of time between the first and sixth fractions, ie. missing radiation doses in the
first week itself, can influence treatment result. This was nearly significantly influenced local
control in the case of T3 tumours treated by the CF. There was a suggestion that it was so
for all T3 tumours, regardless of the schedule. The mean CIFl1_6 in the uncontrolled tumours
was 7.6 days, which means an average prolongation of 0.6 days. This due to the fact that
many T3 tumours which failed had had CIFl1_6 of 8 days or more. Hence treatment missing
by even one day can increase risk of recurrence. This, in turn, suggests that in such tumours
the attempted repopulation may be occurring in the first week of RT itself and interruption at
this juncture favours tumour cell regeneration, and tips the balance in favour of recurrence.
The reversal of the CIFl1_6 result in T2 tumours, though not significant, suggests that T2
tumours are slowly proliferating, possibly with delayed attempts at repopulation. When
considered in terms of the schedule, the CIFl1_6 was seen to be important in CF (albeit in T3
tumours) but not in AF. This is very likely the effect of fraction size, though the influence of
higher AWD can not be ruled out. This can be understood only if regimes giving the same
AWD but different fraction sizes are compared.

In a 5 days/week schedule the planned CIFl1_11 is 14 days. In CC analysis it was found that
when both schedules were combined together there was a significant difference (p
value=0.01) between the controlled and uncontrolled tumours. (Confounding due to combining
two regimes in the analysis could also be present here.) The mean CIFl1_11 in those which
recurred was 15 days, ie. one day more than planned. When taken along with week-end gaps
this means a mean number of 5 missed treatments. This suggests that missing treatments
in the first two weeks is very deleterious. When the schedules were analysed individually it
was seen that with the AF, on the whole, there was no difference. In the T2 tumours treated by AF there was no appreciable difference, but in the T3 tumours the uncontrolled tumours had higher CIFI$_{1,11}$ than the controlled tumours, 14 days and 14.5 days respectively. This means that the uncontrolled tumours had, on average, taken half a day more, which is because quite a few of them must have missed one or more days treatment. Thus it is likely that even with AF missing treatments early during treatment can be deleterious in larger (meaning rapidly proliferating) tumours. In the case of CF uncontrolled tumours had significantly higher mean CIFI$_{1,11}$ than controlled, both overall and in T3 subgroup. Sub-grouping to concurrent BLM showed that in the case of CF+BLM there was no difference in CIFI$_{1,11}$, but in the group not given concurrent BLM, the difference was nearly significant (p value=0.054). This suggests that though missing treatments are deleterious, concurrent BLM may help to overcome this.

Thus the findings from analysis of the CIFI_s suggest that prolongation of CIFI may have different connotations for different tumour types, and is influenced by the schedule. It appears that i.) Missed treatment in the first and second weeks, especially prolongation of the interval between the first and eleventh fractions negatively influences tumour control probability; ii) Such a prolongation is more deleterious in T3 tumours; iii) It may not be very significant in the case of the AF schedule, especially in T2 tumours, but with the CF schedule it is important in tumours of all sizes; iv) Even in CF, effect of prolongation may be cancelled out by addition of BLM. When a tumour is irradiated, it may attempt to undergo division more rapidly and thus attempt accelerated repopulation. Treatment misses at or near this Tk will help tumour repopulation attempts. That CIFI$_{1,11}$ had most significant relation with tumour control suggests that the Tk of most tumours would have been less than 15 days since initiation of treatment. The fact that it was more important in T3 tumours suggest that T3 tumours are more likely to have an earlier Tk than T2 tumours. As the results of the MCHC, tumour duration and other factors show, T3 tumours have a faster growth rate even before treatment. The CIFI findings suggest that they have an earlier Tk. Hence the present study suggest that rapid pre-treatment proliferation and short Tk go hand in hand. The better results in those with lesser than planned CIFI$_{1,11}$, which occurred due to lesser number of week-end gaps, suggests that it is possible that decreasing the CIFI$_{1,11}$ further by avoiding week-end gaps may still improve the results. The lack of a significant effect of CIFI$_{1,6}$ and CIFI$_{1,11}$ in AF is probably due to the greater fraction sizes. It is unlikely to be due to the AWD, again because of the reported lack of superiority of CHART, which delivers a dose of 45 Gy in the period corresponding to the present CIFI$_{1,11}$. The reversal of effect of CIFI$_{1,6}$ and CIFI$_{1,11}$ in T2 tumours may suggest that protraction of treatment may be useful in them. But it will certainly be deleterious to those T2 tumours which happen to have a faster growth rate or ability for a short Tk. The CIFI$_{1,16}$ and CIFI$_{1,21}$ will be influenced by missed treatments in the initial
periods and toxic interruptions too would have started appearing by then. What was interesting was that the dichotomous relation between Tsize and CIFI was present here too. In T3 tumours the CIFI_{1-16} and CIFI_{1-21} was lesser in the controlled tumours, with a trend for significance in the case of CIFI_{1-21}. The relation was reversed in the case of T2. This again suggests that smaller tumours are likely to do better with protraction.

Start DOW

Even though not significant, those pts who had started treatment on a Thursday seems to have done better than those who started treatment on other days, particularly in those treated by CF. Start DOW can influence result because of two reasons: i.) it determines the total number of missed doses of radiation and ii.) It decides the number of treatments that have been delivered before the first (and the subsequent) missed dose occurs. That the first reason is operative is suggested by the fact that CIFI_6 and CIFI_11 were significantly lower in those who started treatment on Thursdays compared to other days. This relationship, in conjunction with the relation between CIFI_{11-11} and local control, reemphasizes the importance of interruptions in the early part of a course of radiotherapy. It is not clear whether the second is operative. That effect will depend on when the tumour attempts accelerated repopulation after start of radiotherapy. Interestingly the other CIFI's, the OTT and the extra-days of OTT were greater in those who started treatment on Thursdays than the other days though the differences were not significant. There is no paradox here if it is understood that pts with least interruption in the first two weeks are more likely to develop intense acute reaction and suffer toxic interruption later on which in turn prolongs the OTT. This finding too underscores the importance of treatment interruption in the initial part of a course of radiation.

The results of analysis of the various time related factors indicate that: i.) OTT per se is not important in determining tumour control with RT, whatever apparent effect is probably due to interruptions in earlier part of the course; ii.) The effect of time is could be in opposite directions for fast and slow growing tumours; iii.) The CIFI in the initial period, particularly CIFI_{1-11}, and to a lesser extent CIFI_{1-6} is important in determining tumour control; iv.) The various time factors was not very important for AF, possibly related to the high fraction sizes of 3.5 Gy may be high enough for week-end gaps not to matter, where as it is really important in CF with fraction sizes of 2.4 Gy; v.) the finding that even CIFI_6 was nearly significant for T3 tumours suggest that they are more likely to start repopulation in the first week of treatment itself.; vi.) some of the time factors operated in reverse direction in T2 tumours suggesting that they mainly consist of slowly repopulating tumours with a delayed Tk and a protracted schedule, but with sufficient fraction size is probably most beneficial for them; vii.) BLM may be useful to counteract effect of prolongation.
in CF; viii) the better results in those with lesser week-end gaps (ie. in those with less than planned CIF_{1.6} and CIF_{1.11}) suggest that it is the inter-fraction interval and the decay of radiation effect during this time, rather than treatment duration per se, that influences tumour control. In a one treatment per day regime the inter-fraction interval is 24 hours. When the week end intervenes, this becomes 72 hours and the effect could have decayed considerably during this time; ix.) the fact that prolonging CIF_{1.6} and CIF_{1.11} did not affect those given treatment with higher fraction sizes indicating that higher fraction sizes may be causing disproportionate or non-linear damage as a result of which the residual damage even after the week-end is over is still quite high. This effect is probably separate from the \( \alpha \) and \( \beta \) kills, because \( \alpha \) kill is linear and \( \beta \) kill is very low or even zero in tumours. An alternative type of cell kill may have to be introduced.

HOST FACTORS

Age

The results of the present study suggest that for cancers of the BGP complex treated by radical radiotherapy age is not a significant factor. There had been reports from this centre that prognosis was poorer in the younger age groups. But the pts included in that series mainly had cancers of the tongue, were treated non-uniformly and had covered younger ages than in the present study. It is also true that the present study has not attempted to analyze whether there are any intrinsic biologic differences among the tumours in the different age groups.

Sex

There are a few reports that the female sex fared better in some head and neck cancers (REF). The present study suggests that it is not so in the case of cancers of the BGP complex.

Erythrocyte Indices

There are no reports on any correlation between erythrocyte indices and tumour size, nor of any such attempts having made. The present study shows that both MCHC and MCH had positive association with Tsize. Pts with larger tumours are more likely to suffer from undernutrition, including iron and protein deficiency, and hence a negative association between these indices and tumour size is expected. But, here, a positive association is seen with pts having higher MCH and MCHC having larger tumours. The association was stronger in those with tumours of shorter duration, but was lacking in those tumours with a long natural
history. Hence it is logical to assume that tumours in pts with high MCH and MCHC are more proliferative, grow fast and attain large size in shorter time. This association can be due to various reasons, but a detailed discussion is beyond the scope of this theses. The reasons can be: I) Higher MCH and MCHC denote more than usual active turnover of red cells. Hence there may be a common systemic abnormality, involving erythropoiesis and iron metabolism, which stimulates the marrow and the tumour cells. Tumour cells which are high in transferrin receptor activity or are able to utilize iron ably for proliferation respond by rapid growth. There are reports on the presence of such abnormalities in cancers. The lower MCHC and MCH in pts with smaller tumours and the lower than normal iron levels in some pts may reflect the body's effort to withhold iron from utilization by the tumour; ii) The tumour may be secreting some factor, such as transferrin, so as to gather more iron which results in stimulation of red cell synthesis too; iii) Both high MCH and rapid growth are secondary to the administration of 'iron tonics' by various doctors, which is a very common practice in Kerala, during the period before final diagnosis (or even after it). Whatever be the cause, this is probably the first report of a host factor directly influencing growth of oral cancers, and of anemia related parameters influencing growth of human solid tumour. As mentioned in the literature review (REF) anemia has been linked to slower growth in animal tumours.

Prognostic influence of Erythrocytic indices

In the present study Hb had absolutely no relation with tumour control, even in large tumours where an association would have been expected since they are more likely to have hypoxic areas, where as the derived indices MCH and MCHC had, especially in large tumours. This can be taken as evidence for the fact that the poor prognosis in anemia and the beneficial effect of higher Hb is not related to the oxygen carrying capacity of Hb. MCH had shown significant positive relation with growth potential of tumours. Hence a significant influence of CIFI\textsubscript{1,6} and CIFI\textsubscript{1,11} was expected in T3 tumours with higher MCH. This was absent. But the association between CIFI\textsubscript{1,6} and CIFI\textsubscript{1,11} and T3 tumour in CF schedule was present in those with lower MCHC. This suggests that high MCH confers to radiotherapy a beneficial effect which over rides the importance of prolongation of CIFI\textsubscript{1,6} and CIFI\textsubscript{1,11}. The beneficial effect conferred by high MCH can be due to two reasons: I.) The increased presence of Hb and the associated intracellular Fe content increases the production of the various free radicals released by radiation interaction by the various mechanisms mentioned earlier (see review of literature); ii) tumours that are associated with MCH related rapid growth rate are likely to have complex cell membranes with high Trf receptor content and Fe bound to these receptors. Such membranes are likely to be more radiation labile and hence such cells are more likely to suffer death by acytokinesis and multinucleation. The action of BLM is mediated through formation of metallo-BLM complexes, especially Fe-BLM complex, and Fe is known
to influence its activity. It also is known to produce injury to cell membrane (REF). Hence it is not surprising that BLM had maximum benefit in those with high MCH. This again supports the contention that effect of high MCH is through mechanisms other than that related to oxygenation. Another reason could be that BLM is more effective in rapidly growing tumours, which pts with high MCH have. This may be because, as mentioned in literature review, BLM can produce injury to cell membrane too. This can contribute to acytokinesis which will be more in faster growing tumours.

The relation of MCH and MCHC to tumour growth and response to radiation can explain some of the paradoxes in the relation of Hb and anemia to radiocurability. Suppose a tumour in a pt with high MCH is rapidly proliferating, it has a higher chance of ‘out growing its blood supply’ and developing hypoxic and necrotic areas. But at the same it can be more radiosensitive too, especially to adequately aggressive schedule, suitable for rapidly proliferating tumours. The present study suggests that when evaluating the effect of tumour hypoxia the erythrocyte indices should be part of the analysis.

SFe, TIBC and %Trf Fe

Even though MCH and MCHC had relation to tumour growth and radiosensitivity, SFe, TIBC and %Trf Fe did not bear significant relationship. This is probably due to the very complex nature of relation of iron metabolism in the host, particularly the host response to the presence of a tumour.

TUMOUR FACTORS

Cytological Indices of Proliferation and Radiosensitivity

The results of the ancillary analysis showed that: I.) Larger tumours in general are more proliferative intrinsically (this is more so for tumours with relatively short history), and small tumours with a long natural history have slow proliferating rate; ii.) Cytologically evaluated MI and CDI are useful indices to identify tumours with intrinsically high proliferative capacity; iii) size in relation to the known duration is possibly a good clinical indicator of proliferative capacity. These findings suggest that large tumours are more resistant not only because they contain larger absolute number of clonogenic cells but also, more probably too, because they have a higher dividing/growth fraction and potential ability to repopulate during radiotherapy. It is possible that the majority of the dividing cells in them have a short cycle time, which can still decrease with radiotherapy.
Inter-relationship of CDI and MCHC

The positive association between MCHC and CDI, though not significant, supports the observed relation between Tsize and MCHC. One reason for the lack of significance is that CDI includes both mitotic and amitotic cells. The amitotic cells do not contribute much to tumour growth since they are essentially non-clonogenic.

Pre-treatment CDI and radiosensitivity

The most probable reason for the lack of relation is that CDI represents both mitotic and amitotic cells. This will have different bearing on radiosensitivity because the clonogenic capacity of these cells are different. The higher values in CF+BLM group represents a selection bias due to the fact that more advanced tumours are generally given chemotherapy.

'SCANC'ing and radiosensitivity.

The results of the 'SCANC'ing suggests that in vivo evaluation of radiation induced nuclear abnormalities by cytology can help to identify tumour radiosensitivity by the second or third week of a course of fractionated radiotherapy. It is in real time, i.e., it evaluates radiation induced damage as and when they occur during treatment. The various radiation induced nuclear abnormalities can be linked to the site and cause of damage which leads to mitotic cell death. Micronuclei are produced by damage to the chromosome and represent both loss of genetic material and abnormal karyokinesis. Injury to PCM or cell membrane causes akaryokinesis and acytokinseis leading to multinucleation (Fig. 25). Whatever be the mechanism of origin of multinucleation the findings of 'SCANC'ing implies that damage to the cytokinetic apparatus is an important factor determining radiosensitivity of oral cancers, probably more important than chromosomal damage. It had also been found that in those tumours which recurred later a balance between cell production and cell kill was reached by around 15 days on an average. An earlier analysis with micronucleation also had suggested that accelerated division can occur even in first week. It is probably the earlier missed treatments including week-end gaps that aid this in such tumours.

Histological subtypes

The present consensus is that verrucous carcinomas are no different from other SCC as regards to control by radiotherapy. This study also suggests the same.
Clinical duration

The duration of the tumour is important since it, along with the proliferation characteristics, determines the T-size at time of treatment. In fact it is the only clinical sign of a rapidly growing tumour. Even though this is recognised, this is never considered as a factor that can affect prognosis. This is mainly because the data has to be elicited from the pt and may not be reliable in the individual pt. The ancillary analysis regarding tumour duration done in the present study confirms that duration alone does not account for the size. Even though not statistically significant, the duration of tumour in the recurred group treated by the CF was less than half that of the controlled group. Analysis also had revealed that those tumours treated by CF schedule were in general larger. In short, with CF schedule, uncontrolled tumours were larger in size and had shorter duration. Since size of a tumour is dependent on two factors, namely its growth rate (which in turn is influenced by the growth fraction and total number of cells) and time since its inception this suggests that uncontrolled tumours treated by CF were so because they were more rapidly proliferating. No such difference was seen in tumour duration between controlled and uncontrolled tumours treated by the AF. This, taken together with other findings, emphasizes that proliferation characteristics influence tumour control and this is schedule dependent.

T-size

Overall, the controlled tumours had a mean size of 3.3 cm whereas the recurrent tumours had a mean size of 3.6 cm, though the difference was not significant (P value 0.07). In the Cross tabulation analysis too there was a nearly significant trend for improved control in smaller tumours, when all pts were considered together. This is just a reflection of the effect of a prescription habit, reflecting the fact that larger tumours, which usually necessitates larger field sizes, had treatment by CF, which entails smaller fraction sizes. This is proved by the fact that the mean size of the tumours treated by CF were significantly higher than those treated by AF.

When analysed separately for the two schedules there was no significant difference in the mean tumour sizes in the pts given CF. But the finding in the case of the AF was interesting. The mean sizes of the controlled tumours were minimally, though not importantly or significantly, larger than uncontrolled tumours in AF. Analysis after categorization to two groups, with cut-off size at 3.5 cm, suggested that in those treated with AF larger tumours did nearly significantly better than smaller.

As discussed earlier, the size of a tumour is dependent on two factors, namely its growth rate and time since its inception. Among tumours with same duration those which have faster
growth rate will be larger. Conversely in any given tumour population larger tumours are more likely to have a higher growth rate. Hence it seems reasonable to suggest that the AF is better for more rapidly proliferating tumours, or, to put it another way treatment failures with AF are not likely to be due to proliferation characteristics but due to other reason. One of this is possibly the lower dose; another is possibly that it is not suitable for tumours with a large Tpot/Tk. It had earlier been suggested (during the discussion on tumour duration) that the CF failures are more rapidly proliferating. Taken together it is not illogical to suggest that the CF is better suited for slowly proliferating tumours and AF is more suited for rapidly proliferating tumours. This is in agreement with the present concept that shorter schedules are better for faster proliferating tumours. But this also calls for a revision of the present concept practice in RCC.

**Invasion of adjacent structures and T-stage**

Invasion of adjacent structures is well established as a factor adversely influencing prognosis. But in the present study involvement of neither skin nor bone influenced treatment result. One reason might be that pts with severe bone involvement are not radical radiotherapy. The more likely reason is given by the significant association between Tsize and invasion, where in larger tumours are more likely to invade adjacent structures. This association can be due to two reasons: i.) Larger tumours had greater duration and hence had greater time available to invade; ii) Larger tumours are more proliferating and such tumours have higher intrinsic ability to invade. Probably both are operative. When all cases were pooled together there was a non-significant trend of poor prognosis for advancing stages (p value=0.11). But when categorized to early (T1&2) and advanced stages (T3&4), Tstage had no obvious impact in either schedule individually. Tstage includes Tsize and invasion. The ancillary analysis suggests that invasion is related to Tsize, and Tsize was shown to essentially represent the proliferative capacity of the tumour. Hence it is possible that the classical relation of advanced Tstages is just reflects proliferative characteristics.

**Lymph node involvement**

Overall there was a nearly significant negative impact of LN involvement on primary tumour control. Such an association has been reported by others too (REF). This can be due to many causes such as: i.) It is proxy effect of tumour size, which is a surrogate for proliferation characteristic and duration, as suggested by the fact that tumours with LN involvement in general had larger Tsize; ii) they have some intrinsic property which makes them inherently radioresistant.
TIME TO RECURRENCE ANALYSIS

The findings of the time to recurrence analysis support the findings of the CC and KM analysis. The recurrences occurring earlier in CF group suggests that rapid proliferation is an important component of such failures. The later failures with AF suggest that lack of radiosensitivity is probably more important than proliferation here. The trend for earlier recurrence in those with shorter natural history suggest that such tumours, especially T3 tumours, are more rapidly proliferating. The same relation between CIFI\(_1\), and time to recurrence, though statistically not significant, emphasizes the fact that repopulation is the cause of failure in those with prolongation during the first 10 fractions. The same relation for the higher CDI group emphasizes the relation between CDI and proliferation. MCH did not have any relation to time to recurrence, even though it is related to tumour proliferation. This obviously is because the higher MCH also confers radiosensitivity.

The findings of the present study suggest that, as opposed to the usual belief, larger tumours with a short natural history do well with aggressive treatment. Since such tumours are likely to start accelerated division soon after initiation of radiotherapy they should be given aggressive short course radiotherapy, preferably with higher fraction sizes and least interruptions. It is even possible that lesser total doses may probably be enough for such tumours provided it is given sufficiently aggressively. A schedule like the AF, giving 50-52.5 Gy in 15-20 days might be most suitable. The converse also is probably true: tumours with small size and longer natural history might do better with more protracted regimes, naturally leading to higher total doses. One example will be a 6 to 7 weeks regime giving total doses of 65-70 Gy. Large tumours with long natural history probably contain cells with varying cell doubling times; they are likely to do best with a regime which, in the initial part of the radiation course, gives high fraction sizes continuously to an intermediate dose and then uses lower fraction sizes to attain reasonably high total dose. A potential strategy will be to give about 35-40 Gy in 15-20 days continuously and then give alternate day treatment to take the total dose to around 70 Gy and the total duration to 7 weeks or so. The decision is difficult in the case of small size and short duration, the proliferation characteristic of which are difficult to predict. The variable dose regime may be most suitable. Pre- and per-treatment cytological evaluation of MI, CDI and other proliferation indices, before treatment and during it will not only help identify proliferation characteristics before treatment but also suggest necessary modifications.
Radiotherapy with concurrent BLM may serve as an alternative to aggressive radiotherapy. Concurrent BLM can be instituted if any forced interruptions, such as due to machine breakdown, occurs or it can be planned earlier if any interruption, such as due to statutory holidays, is anticipated. This will be better than trying to play around with the radiation schedule which will need alterations in total doses, fraction sizes, etc., and may increase morbidity. The long term morbidity with concurrent BLM is acceptable, even if acute reactions are severe.

The proper explanation and understanding of the above, particularly why protraction may be beneficial in slow growing tumours requires a radical change in the concepts of effects of radiation on the tumour, tumour repopulation during radiotherapy and tumour cell kill by radiation.

In the past it was believed that tumour repopulation occurs near the end or after a course of radiotherapy. According to the present concept tumours can repopulate during treatment itself. Repopulation is thought to influence tumour control by increasing the total number of clonogenic cells to be killed. But repopulation during treatment can have another impact. This can be understood by considering what happens when a tissue in which cell death and cell production is actively taking place is irradiated. Under normal circumstances the two processes are equal and balanced, and this can be visualized as a baseline in a time-cell number plot. When such a cell system is exposed to assault by a cytotoxic agent, as soon as the injury is perceived the system responds by stepping up, or rather attempting to step up, proliferation so as to offset the loss due to actual or anticipated cell destruction. If the injury is not sufficient to destroy all the cells capable of renewal this will result in an increase in the number of viable cells and there will be apparent an upward shift in the base line. If the injurious assault does not occur again the cell proliferation will decrease, the base line will come down and the past event will be recognizable as a peak in the base line. The height, width and position of the peak will depend on how fast, how much and how long the response occurs. These will be influenced by the intrinsic properties of the cells, and the nature and severity of the injury. The situation will be different if periodic regular exposure to the agent occurs. Here, if cell destruction predominates, the base line will come down. If the exposure is continued in the same intensity sufficiently long, then all the repopulating cells can get destroyed, at which time the base line will touch zero. If cell repopulation exceeds cell destruction a new base line at a higher than pre-exposure level will occur, in which case, when the exposure is finally stopped, there will be more proliferating cells than before the exposure. Again the factors which determine the final course of events will be the intrinsic capacity of the cells to divide, the dose of the agent and the severity of the and damage, and whether there are any missed exposures. Radiation is an injurious agent and it is not difficult
to imagine the above sequence of events taking place during fractionated radiotherapy of a tumour. If a treatment is missed, whether scheduled, unscheduled or weekend, then, if the tumour cells are actively dividing, cell production will gain an upper hand and the likelihood of a higher baseline being reached will increase that much. A missed treatment may not matter if the tumour cells are not actively dividing at that time. The fact that in the present study the CIFI \(_{1,11}\) had the strongest relationship with tumour control suggest that most of the tumours would have started active repopulation before day 15. The fact that even week end gaps can affect treatment results is suggested by the finding that those with CIFI \(_{1,11}\) less than fourteen days had better results than those with CIFI \(_{1,11}\) of fourteen days, the scheduled time. Also those who had treatment started on a Thursday had better results, the only reason being that missed doses due to week-end gaps were lesser in them.

One question that the finding on CIFI raises is whether it is important that radiation be present during the time the cells are proliferating or whether it is enough that sufficient dose be pushed in before the tumours start repopulating. The second view formed the basis of the design of the CHART regime in which the scheduled dose is given in 12 days. But its success never reached the expectations it raised. The offered explanation for this lack of success is that the total dose was low, being only 54 Gy, especially for hypoxic cells. But this may not be the reason because the AF in this study, which gave quite good results, delivers a total dose of 52.5 Gy which is less than that of CHART. Its main difference from CHART is that the fraction sizes are higher and the OTT is greater. Based on these an alternative explanation is easy if it can be assumed that presence of radiation is essential at the time of cell division or shortly before it. The CHART accumulates quite high doses in the initial period itself, but there is no radiation after 12 days. Since a majority of tumours start repopulating early during the treatment, CHART would have covered those which do so with in this period. But in each tumour it will miss the cells that divide at later times and of course all tumours which start accelerated division at later times. This will ascribe failure of CHART as due to giving too much dose too early with no radiation later. Additionally it is possible that fraction sizes are important for tumour cell kill too. The findings from assay on nuclear changes show that damage to kinetic structures and resultant amitosis, especially interference with cytokinesis, is important in cell kill by radiation. The damage to kinetic structures could be fraction size dependent ie. large fraction sizes may cause disproportionate injury. The AF in this study used fraction sizes of 3.5 Gy which is more than double the 1.5 Gy with CHART. This might be another reason for the better success of the AF. Another reason could be that the OTT with AF was greater than that with CHART and hence it would have covered some of those tumours which start repopulating in the third week. CHART was not inferior to conventional schedules only because most tumours probably start repopulating at early periods. It is possible that kinetic structures recover from injury during inter-fraction intervals. In that case
the residual damage after any interval will be more in schedules using larger fraction sizes, i.e., prolonged inter-fraction interval will affect them less. This might be one reason why the CIF1,11 did not influence tumour control in the case of AF. The fraction size of 2.4 Gy obviously is not large enough to cover week-end gaps and interruptions, hence CIF1,11 significantly is associated with tumour control in those treated with CF. This supported by the fact that results with continuous 7 day schedules are reported to be very excellent (REF). In the case of CF it is possible that some fast proliferating tumours could have escaped because of the week-end treatment misses; thus bringing down the control rates. This is shown by the fact that local control with CF is significantly less than with the AF, even in those pts with CIF1,11 equal to or less than scheduled. It is possible that the results with CF would have improved remarkably if all interruptions, including week-end gaps, were avoided. This is suggested by the finding that results were better in those with CIF1,11 less than that scheduled. It achieved at least this much success probably because it covered some late proliferating tumours since the OTT is greater. This may account for many of the failures in AF, as suggested by the finding that AF is less successful in T2, in those with greater duration and the higher OTT and CIF1 in some sub-groups.

These findings taken in conjunction with the others such as the better effect with higher fraction size, importance of CIF1,11, etc. suggest that presence of radiation at or some time before cell division, especially cytokinesis, may be important in tumour cell kill. This then will mean that for tumours with a delayed Tk, a short course regime such as the CHART may not at all serve the purpose. It is possible that at least some of the failures of the AF may be due to this. The presence of such tumours in a given population can account for higher success with higher total doses. This can be explained by contemplating what happens when a tumour consisting of cells (or a population of tumours), with Tk ranging from one day to 50 days, are irradiated continuously, daily, with a daily dose of 2Gy. Assume also that on each day 2% of the initial number of cells attempt division and that each fraction kills that a major fraction of the cells dividing that day by producing acytokinesis. In this case as the number of days that irradiation is given increases the TCP increases and
once 50 days of irradiation is over the TCP will be near 1. A dose-response plot will present the picture that it is the increase in dose that increases TCP and a TCP of around 1 is achieved at a dose of 100Gy, when in reality the total dose has nothing to do with it. If any irradiation is missed the cells that would have been killed that day succeed in dividing and the whole relationship with TCP can go hay-wire. The idea presented is of course too simplistic, but it is also possible that something similar may be happening in cancer radiotherapy. In fact cell kill by interference with kinetic apparatus of the cell may be recognised as a new type of cell kill, distinct from $\alpha$ and $\beta$ type of kills which are due to DNA damage, may be introduced. This can be best termed as $\kappa$ kill, for kill by kinesis interference. Better effect with high fraction size schedules such as the AF can be explained if it is assumed that effect of fraction size on $\kappa$ kill is not linear, and recovery from $\kappa$ injury can take place during inter-fraction intervals. The existence of $\kappa$ kill, its fraction size dependence and recovery during inter-fraction intervals, along with the assumption that most tumours have an early Tk falling with in 20 days of start of treatment can explain many inconsistencies and paradoxes in fractionated radiotherapy. It can explain why higher doses give higher TCP, why aggressive short course regimes are not successful, why regimes which give continuous radiation for a reasonably prolonged time are very successful, why OTT per se is not important, why larger tumours with potentially early Tk do better with short course intensive regimes which are not more successful than conventional fractionation in smaller tumours, why fractionated radiotherapy is better than single high doses, etc. It, in essence, is suggested that proliferation and radiosensitivity are not independent determinants of tumour control; it is the attempted proliferation during the time of radiation or when the effect of radiation still lingers that causes death of the cell. The concept of "proliferation related radiosensitivity" is more valid than the present day concept which attributes all cell kill to DNA damage.