Synchronous Chemo-radiation in Early Stage Breast Cancer: A Review of the World Literature

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In 1996 a study published in the *New England Journal of Medicine* by Recht and colleagues [1] from Boston, USA, suggested that delaying radiotherapy until after chemotherapy may lead to a higher rate of local recurrence (14 v 5%; Table 1). However, delaying chemotherapy until after radiotherapy may result in an increased rate of distant metastases (32 v 20%). A subsequent overview by Huang et al [2] showed a five-year local recurrence rate of 6% when radiotherapy was given first compared with 16% when delivered after chemotherapy. This paper was criticised because it omitted several key studies. Notably, it was written in 2003 before the update from the Boston group [3], which showed that the initial differences observed in the Recht et al study had disappeared with longer follow-up (Table 1). There seems to be no randomised data to suggest that there is any advantage in giving radiotherapy prior to the delivery of chemotherapy.

Table 1. Results from the Boston Group

	Site of First Recurrence			
Follow-up	**5 years [1]**		**11 years [3]**	
	Local	**Distant**	**Local**	**Distant**
RT⇒CT	5%	32%	13%	32%
CT⇒RT	14%	20%	15%	26%

This begs the question as to whether there is any advantage in giving synchronous chemo-radiation to the standard treatment of chemotherapy followed by radiotherapy. To date three studies have been formally published, two from France (Table 2).

The largest of these is the Arcosein trial [4], in which patients were randomised to either six cycles of 5-fluorouracil, mitoxantrone, and cyclophosphamide (FNC) with either concurrent or sequential radiotherapy. The study showed no difference in overall five-year disease-free survival or loco-regional free survival, but there was a five-year loco-regional free survival advantage to the synchronous group in a very small sub-group of node-positive patients (synchronous arm: 97%, seven recurrences; sequential arm: 91%, 17 recurrences; $p = 0.02$). In terms of local recurrences there were 7.3% in the sequential arm and 4.5% in the synchronous arm (see Table 2). Significantly increased toxicity occurred in the synchronous arm, both in terms of acute skin reaction and late effects including fibrosis, telangiectasia and breast atrophy.

The second study by Rouëssé and colleagues [5] used two different chemotherapy regimes, 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for the sequential arm and FNC for the concurrent radiation arm. They found no difference in disease-free survival between the two arms, but there was a benefit in local control in the synchronous arm of 3% (nine recurrences) versus 7% (20 recurrences), $p = 0.047$. The benefit was seen predominantly in patients who had undergone a lumpectomy. Again there was an increase in acute skin toxicity, cardiac toxicity, myelotoxicity and telangiectasia. There was an increased risk of second malignancies in both studies, including leukaemia in both arms. [N.B. mitoxantrone-containing chemotherapy regimens are no longer used in the adjuvant treatment of breast cancer.]

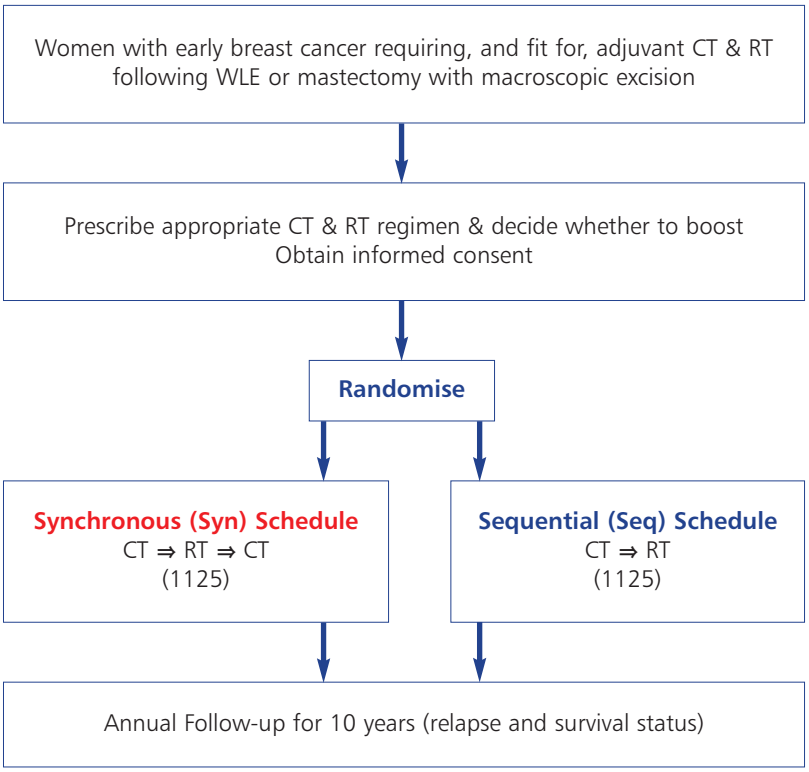
Arcangeli et al. [6] also published a randomised trial, using cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy. Only 206 of the planned 400 patients were entered into the trial because of poor recruitment and there were only two events in each arm. Interestingly, however, there were no significant cases of acute skin toxicity or radiation pneumonitis despite using concurrent full doses of radiation and chemotherapy treatment.

From these studies and the Cochran overview [7],

Table 2. Five Year Local Recurrence Rates Reported in Randomised Trials of Sequencing of Chemo-radiation in Early Breast Cancer

	Arcosein [4]	**Rouëssé et al. [5]**	**Arcangeli et al. [6]**
	n=716	n=650	n=206
Sequential CT⇒RT	7.3% (n=25)	7.0% (n=20)	2.0% (n=2)
Synchronous CT⇒RT⇒CT	4.5% (n=16)	3.0% (n=9)	1.9% (n=2)
Notes: Type synchronous CT & RT Chemotherapy regimen Radiotherapy schedule	Concomitant FNC 50Gy in 25F	Concomitant Seq FEC & Syn FNC 45-50Gy in 20-25F	Concomitant CMF 50Gy in 25F & boost

Figure 1. SECRAB Trial Design.



synchronous chemo-radiation in early stage breast cancer had not been considered beneficial. The preliminary results of the SECRAB (Sequencing of Chemotherapy and Radiotherapy in Adjuvant Breast cancer) trial presented at European Cancer Congress in September 2011 changed this perception [8].

SECRAB was a prospective, UK, multicentre study in which patients were randomised to synchronous or sequential therapy (Figure 1). Patients could only be treated with CMF or anthracycline (A or E) followed by CMF. A variety of different radiotherapy schedules were used and, for simplicity, were split into those of three weeks duration (15 fractions) or > 3 weeks (> 15 fractions).

Of the 2,296 recruited women, and with a median follow-up of 8.8 years, we found 63 and 41 local relapses in the sequential and synchronous arms, respectively. Five-year local relapse rates were 5.1% for the sequential arm compared with 2.8% for the synchronous arm. Synchronous treatment was significantly beneficial, with a 35% reduction in the risk of local recurrence (HRSyn = 0.65, 95% CI: 0.44, 0.96; p = 0.03) [8].

There was an increase in acute skin toxicity and telangiectasia in patients treated with synchronous treatment, this was seen mainly in patients having > 3 weeks of radiotherapy. However, there was no difference in other late effects, including pneumonitis, lymphoedema, rib fracture, brachial plexopathy, severe subcutaneous fibrosis and cardiac events [9]. There was no difference in dose intensity of chemotherapy [9], quality of life [10] or overall survival (83% synchronous arm v 82% for the sequential arm) [11]. We await results of cosmetic evaluation before this can be considered a standard treatment.

These results are applicable to CMF containing regimes. It may be time to look again at how to combine radiotherapy with regimens such as E-CMF, E-T-CMF, A-CMF or A-T-CMF (where T represents taxane), which seem to be at least as effective as standard FEC or FEC-T, but have the advantage that synchronous chemo-radiation could be used as part of the treatment protocol. ■

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Chemoradiation in breast cancer: A new treatment option?