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Neoadjuvant Treatment for Oesophago-Gastric Cancer

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1. Introduction

In the United Kingdom, oesophageal cancer ranks as the ninth most common cancer with a rising incidence of 13 per 100,000 head of population. Some two-thirds of all oesophageal lesions are adenocarcinomas, the rest are squamous cell carcinomas. The incidence of stomach cancer is similar but a decline has been registered over the past two decades. For both conditions the age at presentation is 60 years or more in over two-thirds of patients. Tumours of the oesophago-gastric junction have received detailed attention over the past years. This is in part because surgical excision through a single operative field may not be possible. Moreover, for this subset of lesions, a rising incidence and worse survival have been registered.

Oesophago-gastric malignancies carry a poor prognosis especially when diagnosed at an advanced stage outside screening programmes. In Western countries, this is reflected as overall five year-survival rates ranging from 5 to below 20%. Over the years, treatment has evolved into a multi-modality strategy which is best formulated and overseen in a multidisciplinary setting. The treatment of an individual patient will depend on accurate and reliable tumour staging, assessment of the patient's fitness for radical surgical and/or oncological treatment, the level of expertise available locally and, of course, the patient's informed decisions. In a typical surgical unit in the United Kingdom, resection rates will not usually surpass 20%.

After radical surgery with curative intent the median disease free survival is of the order of two years with 50% of cases developing metastases and/or recurrence in the first year. These disheartening figures offer the rationale for the addition of further oncological treatment to radical surgery. Neoadjuvant chemotherapy and/or radiotherapy is administered before surgery with the aim of shrinking the primary tumour and theoretically ablating micro-metastases and reducing the risk of haematogenous and lymphatic dissemination. This treatment, however, has the potential for toxicity and complications and must be used carefully in patients with co-morbidity. There are concerns that pre-operative treatment may influence the patient's ability to withstand the surgical insult and the percentage of patients who are fit enough to complete post-surgical treatment regimens is also diminished.

This chapter will review the main influential randomised trials employing neoadjuvant treatment for these cancers. It will also comment on the other randomised and non-randomised series published in the literature focusing on the effect of treatment on resectability, peri-operative morbidity and mortality, resection specimen pathological

stage and completeness of excision and longer-term outcomes. Finally, future prospects will be explored.

2. Neoadjuvant radiotherapy for oesophageal cancer

Preoperative radiotherapy in oesophageal cancer patients aims to reduce tumour size, decrease the extent of localised microscopic residual disease and lower the risk of tumour dissemination at the time of surgery. The first published study suggesting that such treatment may improve survival for this group of patients was by Kakyama et al in 1967. The study reported a 5 year survival rate of 37.5% for the group receiving preoperative radiotherapy compared with 19.1% 5 year survival rate in the surgery alone arm. The criticisms of the study are that it was retrospective with no statistical analysis of the data. During the 1980's and early 1990's five randomised controlled trials were published comparing neoadjuvant radiotherapy and surgery alone (Launois et al 1981, Gignoux et al 1987, Wang et al 1989, Arnott et al 1992 and Nygaard et al 1992). All these studies except for Arnott et al were restricted to treating squamous cell carcinoma. Radiation doses ranged from 20Gy to 40Gy and were given over a period of eight to twenty eight days. A summary of the five trials is shown in Table 1.

Study	Tumour histology	Treatment	n	Percentage of patients alive at 5 years
Launois et al 1981	SCC	Surgery alone	57	11.5
		Pre-op radiotherapy + Surgery	67	9.5
Gignoux et al 1987	SCC	Surgery alone	102	11
		Pre-op radiotherapy + Surgery	106	10
Wang et al 1989	SCC	Surgery alone	102	30
		Pre-op radiotherapy + Surgery	104	35
Arnott et al 1992	SCC & Adeno	Surgery alone	86	17
		Pre-op radiotherapy + Surgery	90	9
Nygaard et al 1992	SCC	Surgery alone	41	9
		Pre-op radiotherapy + Surgery	48	21

Table 1. A summary of neoadjuvant radiotherapy studies. SCC – squamous cell carcinoma. Adeno – adenocarcinoma.

None of the trials proved any significant improvement in 5 year survival. However, Nygaard et al 1992 did report 3-year survival rates of 20% in those patients receiving preoperative radiotherapy compared to 5% in the surgery alone arm. This improved survival was only achieved after pooling data from the radiotherapy group with patients receiving preoperative chemo-radiotherapy and did not prove to be statistically significant.

Each of the five trials mentioned contained relatively small numbers of patients. Therefore in order to investigate any small benefit afforded by preoperative radiotherapy, data from all 1147 patients were used in a meta-analysis published by Arnott et al 1998. This study again showed there was no clear evidence that preoperative radiotherapy improves the survival of patients with potentially resectable oesophageal cancer [hazard ratio (HR) 0.89; (95% CI 0.78 -1.01); $p=0.062$].

To date there have been no new studies published relating to neoadjuvant radiotherapy (Cochrane Review, Arnott et al 2010).

3. Neoadjuvant chemotherapy for oesophageal and gastric cancer

Chemotherapy aims to downstage tumours and remove distant micro metastasises. There have been many randomised controlled trials comparing overall survival of oesophageal cancer patients receiving neoadjuvant chemotherapy followed by surgery with surgery alone (Roth et al 1988, Nygaard et al 1992, Schlag et al 1992, Maipang 1994, Law 1997, Kelsen 1998, Acona 2001 and The UK Medical Research Council (MRC) trial 2002. The two largest of these studies are by Kelsen et al 1998 and the MRC trial of 2002.

Kelsen et al enrolled 440 patients with resectable oesophageal cancer that included squamous cell carcinoma, adenocarcinomas and undifferentiated tumours. The patients were randomised into two groups.

The surgery alone group numbered 227 patients who had primary surgery. The chemotherapy arm of the trial consisted of 213 patients. Both underwent the same surgical procedure. Surgical mortality was similar in each group, 10% in the chemotherapy arm and 13% in surgery alone group.

The patients in the chemotherapy arm received three cycles of cisplatin and fluorouracil before surgery. 71% of patients completed all three cycles. 7% of patients showed a complete clinical regression while 12% achieved a partial regression. Complete responses (T0N0M0) were found in 2.5% of patients.

Following chemotherapy 133 patients went on to have a R0 resection. This sub group was due to receive two post-operative cycles of chemotherapy, however, only 32% completed both courses due to patient or physician choice.

Overall median survival in the surgery alone group was 16.1 months compared to 14.9 months in the chemotherapy group ($p=0.53$). Two year survival was 37% and 35% respectively ($p=0.74$). There was no difference in outcome between patients with adenocarcinoma and squamous cell carcinoma. Among patients whose resection was curative, there was no significant difference in survival between those who did and those who did not undergo chemotherapy (median survival, 27.4 and 25 months, respectively). Kelsen et al concluded that neoadjuvant chemotherapy did not improve survival in oesophageal cancer. It must be noted that the operative mortality in this study is higher than would be deemed acceptable at present (less than 5%).

Kelsen et al 2007 published an update on their 1998 paper in which they looked at the longer term survival of the same group of patients. This again showed no difference in overall survival between patients receiving preoperative chemotherapy compared to those receiving surgery alone although patients with objective tumour regression after preoperative chemotherapy did have an improved survival. The paper also evaluated failure patterns on the basis of completeness of resection, concluding that only R0 resection results in substantial long term survival irrespective of whether neoadjuvant chemotherapy is given.

Like Kelsen et al the MRC study was a multi-centre trial recruiting patients suffering from either adenocarcinoma or squamous cell carcinoma of the oesophagus. 802 patients took part and were randomised into two groups, surgery alone n=402 and preoperative chemotherapy plus surgery n=400. Two cycles of chemotherapy were given using cisplatin and fluorouracil. Unlike Kelsen's study, the MRC trial allowed clinicians to give patients preoperative radiotherapy (25-32.5Gy). Nine percent of patients in both groups received radiotherapy.

Of the 400 patients assigned to the chemotherapy arm, 372 received chemotherapy, 350 completed two cycles while 22 patients only completed one. Pathological data from the resected specimens showed that patients who received preoperative chemotherapy had smaller tumours ($p=0.0001$) that extended less frequently into surrounding tissue and showed less lymph node involvement than tumours in the surgery alone group. Nodes at any site were involved in 195 (58%) of the chemotherapy group and 216 (68%) of the surgery alone patients ($p=0.009$).

Median survival in the chemotherapy group was 16.8 months compared with 13.3 months in the surgery alone group. Two year survival rates were 43% compared with 34%, respectively. There was no evidence to suggest that the effect of chemotherapy varied in accordance with histology. The MRC trial concluded that overall survival was better in the neoadjuvant chemotherapy group than the surgery alone group (HR 0.79; 95% CI 0.67–0.93; $p=0.004$) with an estimated reduction in risk of death of 21%.

Critics of the MRC study suggest that the inclusion of patients receiving preoperative radiotherapy as well as neoadjuvant chemotherapy may be the cause for the improved survival in the chemotherapy group. However, the estimate of treatment effect on overall survival was not altered by removal of those patients from the analysis who received preoperative radiotherapy; hazard ratio for the 728 patients (364 CS, 364 S) who did not receive radiotherapy was 0.78 (95% CI 0.66–0.93; $p=0.005$). In the chemotherapy group compared with the surgery alone group, more patients were alive without residual or recurrent disease ($p<0.0001$).

In 2009 the long term results of the MRC 2002 trial were published. This paper confirmed that survival benefit was maintained in the chemotherapy group with a hazard ratio of 0.84 (95% CI, 0.72 to 0.98; $p=0.03$) which in absolute terms is a 5-year survival of 23.0% for chemotherapy group compared with 17.1% for surgery alone patients. The study also showed that the treatment effect is consistent in both adenocarcinoma and squamous cell carcinoma (Allum et al 2009).

As well as the MRC 2002 and Kelsen study six other smaller randomised control trials have compared survival between oesophageal cancer patients receiving surgery alone or neoadjuvant chemotherapy plus surgery. These additional studies are listed in Table 2 and all contain small numbers of participants.

Study	CS, number of patients	S, number of patients
Roth et al 1988	19	20
Nygaard et al 1992	56	25
Schlag et al 1992	22	24
Maipang et al 1994	24	22
Law et al 1997	74	73
Kelsen 1998	233	234
Ancona et al 01	48	48
MRC 02	400	402
Total	876	848

Table 2. Randomised control trials comparing surgery alone (S) vs neoadjuvant chemotherapy plus surgery (CS) for the treatment of resectable oesophageal cancer.

Combining the data from all eight studies in a meta-analysis would increase the ability to detect an improved survival rate. Furthermore any benefit from preoperative chemotherapy relating to the specific histological subtypes could be more effectively elucidated. GebSKI et al 2007 undertook such a meta-analysis pooling data from 1724 patients. The results showed an overall benefit of giving preoperative chemotherapy (HR 0.9; 95% CI 0.81-1.00; $p=0.05$), equating to a survival benefit of 7% at 2 years. The treatment effect of neoadjuvant chemotherapy relative to tumour cell type indicated that patients with squamous cell carcinoma gained no benefit from preoperative chemotherapy (hazard ratio for mortality 0.88 (95% CI 0.75-1.03; $p=0.12$). However, quite the opposite was the case for those with adenocarcinoma, who gained a significant benefit from neoadjuvant chemotherapy (hazard ratio for mortality 0.78 :95% CI 0.64-0.95: $p=0.014$).

Further evidence that neoadjuvant chemotherapy improves survival for patients with adenocarcinoma comes in the form of the MRC MAGIC Trial (Cunningham et al 2006) which evaluated the survival benefits of giving preoperative epirubicin, cisplatin, and infused fluorouracil (ECF) in patients with gastric and oesophagogastric adenocarcinomas.

In brief, the study recruited 503 patients with resectable adenocarcinoma of the stomach, oesophagogastric junction or lower oesophagus. Of the 503 patients approximately 26% had a tumour of the lower oesophagus or gastro-oesophageal junction. The patients were randomised to receive either preoperative chemotherapy plus surgery $n=250$ or surgery alone $n=253$. Three cycles of ECF were given preoperatively to the chemotherapy group followed by three further cycles postoperatively. Only 41.6% of the group completed all six cycles.

Pathological examination of the resected specimens confirmed significantly smaller tumour diameters in the chemotherapy group compared with the surgery alone group ($p<0.001$). The chemotherapy patients also had a higher proportion of T1 and T2 tumours than the surgery group ($p=0.002$) while those patients with gastric cancer showed a significant trend to less advanced nodal disease ($p=0.01$) which suggests tumour shrinkage or 'down staging' within the chemotherapy group.

On final analysis the chemotherapy group had a significantly higher likelihood of progression-free survival (HR 0.66; 95%CI 0.53 to 0.81; $p<0.001$) and of overall survival (HR 0.75; 95% CI 0.60 to 0.93; $p=0.009$) which translates into 5 year survival rates of 36.3% for the chemotherapy group and 23% for the surgery alone group. Importantly there was no

clear evidence of heterogeneity of treatment effect according to the site of the primary tumour, age group, sex, or the WHO performance status. These results lead to the trial concluding that preoperative ECF chemotherapy improves overall and progression-free survival among patients with resectable adenocarcinoma of the stomach, lower esophagus, or gastroesophageal junction, as compared with surgery alone.

Li et al 2010 performed a meta-analysis of 14 trials of neoadjuvant chemotherapy for gastric cancer (including of course the MAGIC trial). This study distils some very important aspects of the rationale for preoperative treatment and clearly reports some conclusions based on large numbers of patients. A total of 2271 patients (1054 in the neoadjuvant group and 1217 in the surgery only group) were analysed with a median follow-up period of 54 months. Table 3 outlines the main conclusions.

Parameter	Number of studies	Effect (CS vs S)
Overall survival at 3 years	12	48.1% vs 46.9%, favouring CS NNT - 84
Progression free survival at 3 years	3	41.1% vs 27.5%, favouring CS NNT - 8
Tumour downstaging	6	49.9% vs 37.5% for T0-2 favouring CS NNT - 9
R0 resection rate	8	75.2% vs 69.9%, favouring CS
Perioperative mortality	3	5.4% vs 4.6%, equivalent
Subgroup analyses	n/a	Effect on overall survival higher for T3 and T4 lesions Effects higher in Western studies Monotherapy inferior to multiple drug regimens IV route better than others

Table 3. Conclusions from the meta-analysis of neoadjuvant chemotherapy for gastric cancer by Li et al 2010. CS - neoadjuvant, S - surgery only, n/a not applicable, NNT - numbers needed to treat, IV - intravenous administration.

4. Neoadjuvant chemo-radiotherapy for oesophageal cancer

Neoadjuvant chemo-radiotherapy aims to downstage tumours preoperatively and reduce the risk of both local and distant metastatic recurrence. There has been great interest in this area with nine randomised control trials comparing overall survival between patients receiving neoadjuvant chemo-radiotherapy plus surgery (CRTS) and surgery alone (S) in oesophageal cancer patients. Table 6 summarises the treatment regimens while Table 7 shows the overall mortality estimates for each trial.

As shown in Tables 4 the numbers of patients taking part in each chemo-radiotherapy trial is relatively small. Treatment regimens also differ with radiation doses ranging from 20 to 50.4 Gy given either concurrently with the chemotherapy or sequentially which would reduce radiosensitisation of the tumour. The type of chemotherapeutic agents administered also varies. However, in the majority of trials, this is in the form of cisplatin (20-100mg/m²) and 5-fluorouracil (300-1000mg/m²).

Trial	Cell Type	CRTS n	S n	CRT Treatment	Sequential or Concurrent radiotherapy	Hazard Ratio (95% CI)
Nygaard et al 1992	SCC	53	25	Cisplatin, Bleomycin & 35Gy	Sequential	0.76 (0.45-1.28)
Apinop et al 1994	SCC	35	34	Cisplatin, 5FU & 40Gy	Concurrent	0.80 (0.48-1.34)
Le Prise et al 1994	SCC	41	41	Cisplatin, 5FU & 20Gy	Sequential	0.85 (0.50-1.46)
Walsh et al 1996	Adeno	48	50	Cisplatin, 5FU & 40Gy	Concurrent	0.58 (0.38-0.88)
Bosset et al 1997	SCC	148	148	Cisplatin & 37 Gy	Sequential	0.96 (0.73-1.27)
Urba et al 2001	Adeno & SCC	50	50	Cisplatin, 5FU & 45Gy	Concurrent	0.74 (0.48-1.12)
Lee et al 2004	SCC	51	50	Cisplatin, 5FU & 45.6Gy	Concurrent	0.88 (0.48-1.62)
Burmeister et al 2005	Adeno & SCC	128	128	Cisplatin, 5FU & 35Gy	Concurrent	0.94 (0.70-1.26)
Tepper et al 2008	Adeno & SCC	30	26	Cisplatin, 5FU & 50.4Gy	Concurrent	0.40 (0.18-0.87)
Walsh et al 1995,unpublished	SCC	29	32	Cisplatin, 5FU & 40Gy	Concurrent	0.74 (0.46-1.18)
Total		623	586			0.81 (0.70-0.93)

Table 4. Summary of treatment given in chemo-radiotherapy trials & overall mortality estimates for neoadjuvant chemo-radiotherapy compared to surgery alone. SCC- Squamous cell carcinoma, Adeno - Adenocarcinoma, CRTS - Chemo-radiotherapy+Surgery, S -Surgery alone, CRT - Chemo-radiotherapy

Although most of the trials suggest there is benefit from giving preoperative chemo-radiotherapy, only two show a significant benefit in terms of overall mortality when compared to surgery alone. These studies are those by Walsh et al 1996 (HR 0.58;95% CI 0.38-0.88) who only enrolled adenocarcinoma patients and Tepper et al 2008 (HR 0.40; 95% CI 0.18-0.87) who included approximately 25% squamous cell carcinoma patients.

In order to shed more light on the effect of chemo-radiotherapy two recent meta-analyses have been published GebSKI et al (2007) and Jin et al (2009).

GebSKI et al using the pooled data showed that there was a relative reduction in mortality for patients receiving neoadjuvant chemo-radiotherapy (HR 0.81; 95% CI 0.70-0.93; p=0.002)

and that there was no evidence of heterogeneity between the trials or any temporal effect. GebSKI et al. went on to look at the survival benefit of chemo-radiotherapy for the different tumour cell types. Patients with adenocarcinoma were shown to benefit (HR 0.75; 95% CI 0.59–0.95; $p=0.02$) while those with squamous cell carcinoma receiving sequential radiotherapy gained no survival advantage (HR 0.9; 95% CI 0.72–1.03; $p=0.18$.) However, when radiotherapy was administered concurrently a significant survival benefit was seen in squamous cell carcinoma patients (HR 0.76; 95% CI 0.59–0.98; $p=0.04$).

Jin et al 2009 using the same data as GebSKI et al (plus the addition of a trial by Natsugoe et al 2006 containing 55 patients) also concluded that oesophageal cancer patients gain a survival benefit from receiving neoadjuvant chemotherapy Odds Ratio (OR) 1.78 (95% CI 1.20–2.66, $p = 0.004$) for 3 year survival. The paper goes on to state that there is no survival benefit from chemo-radiotherapy for those patients with squamous cell carcinoma (OR 1.34; 95% CI 0.98–1.82; $p = 0.07$) for 3-year survival implying only adenocarcinoma patients benefit. This should be treated with caution as odds ratios have been superseded by hazard ratios as a more reliable method of survival analysis. Furthermore, Jin et al 2009 suggest that the p value of 0.04 for the hazard ratio relating to concurrent chemo-radiotherapy providing survival benefit for SCC patients in GebSKI et al meta-analysis is not significant. However, an important point made by Jin et al is that the post-operative mortality of chemo-radiotherapy patients is significantly higher than those receiving surgery alone (OR: 1.68, 95% CI: 1.03–2.73, $p = 0.04$). This point was also noted in the meta-analysis by Fiorica et al (2004).

5. Conclusion

To date, no randomised control trial has shown any survival benefit from neoadjuvant radiotherapy in the treatment of resectable oesophageal cancer. A number of trials have suggested preoperative chemotherapy could improve survival (Roth et al 1988, Law et al 1997, Ancona et al 2001 & MRC 2002) However, only the MRC 2002 and MRC MAGIC trial 2006 (only 26% of which had lower oesophageal/gastro-oesophageal junction tumours) showed a small improvement that was statistically significant. For chemo-radiotherapy, the studies by Walsh et al (1996) and Tepper et al (2008) are the only two trials to show a significant survival benefit.

All the trials investigating neoadjuvant chemotherapy or chemo-radiotherapy were small in size, often lacking the power necessary to detect small differences between groups. In order to detect a small yet worthwhile benefit from these different treatment modalities, data have been pooled for meta-analysis. The most comprehensive of these by GebSKI et al (2007) showed an overall survival benefit from neoadjuvant chemo-radiotherapy of 13% at two years and a benefit of 7% at two years from preoperative chemotherapy. When looking at histological subtypes; chemo-radiotherapy improved survival for both adenocarcinoma and squamous cell carcinoma patients; chemotherapy also improved survival in those with adenocarcinoma however, no benefit was shown for patients with squamous cell carcinoma. Although chemo-radiotherapy has been shown to provide the greatest survival benefit, it has been associated with a higher post-operative mortality (Fiorica et al 2004 & Jin et al 2008). As a consequence, clinicians are still divided as to which treatment would be best for their patients. In this chapter, the majority of trials discussed have employed cisplatin and 5-FU. However, the doses and radiation given to those patients receiving chemoradiotherapy have varied, which makes comparisons between trials more difficult. All the randomised control trials were designed over a decade ago. Since then, new chemotherapeutic agents have become

available and the delivery of radiotherapy has also advanced. In recent years the use of taxanes, when given concurrently with radiotherapy in the treatment of non-small cell lung cancer, have shown potential (Choy et al 1998, 2000 & Lau 2001). In a phase II trial, Van Meerten et al (2006) used Paclitaxel and Carboplatin with concurrent radiotherapy (total dose 41.4Gy) in oesophageal cancer patients with encouraging results. The CROSS trial uses the same chemo-radiotherapy regime in a phase III randomised control trial comparing neoadjuvant chemo-radiotherapy followed by surgery with surgery alone for surgically resectable oesophageal adenocarcinoma and squamous cell carcinoma (Van Meijl et al 2008).

After the encouraging results of both the MRC 2002 and MAGIC trials further investigation of neoadjuvant chemotherapy to treat oesophageal cancer in the form of the OE05 trial are ongoing. OE05 is a randomised control trial comparing standard neoadjuvant chemotherapy (2 cycles of cisplatin + 5FU) with neoadjuvant ECX (4 cycles of Epirubicin, Cisplatin and Capecitabine) (OE05 clinical protocol 2008). The results of both trials are keenly awaited.

The major drawback with chemotherapy and chemo-radiotherapy lies in that both treatments are non-specific for the tumour or metastases they are targeting. A significant amount of non-malignant tissue is injured by both forms of treatment. In an attempt to fine tune the delivery of radiotherapy brachytherapy has been used in the palliative treatment of patients with advanced luminal oesophageal cancer. Overall survival at one year was 19.4% (Sur et al 1998). More recently, immunotherapy in the form of tumor-infiltrating lymphocytes (TILs), tumour vaccines and adoptive T-cell immunotherapy, which specifically targets tumour cell surface antigens using a chimeric immune receptor have been developed. Specific targeting would reduce damage of non-malignant tissue, could have the ability to down stage tumours preoperatively, mop up any residual micro metastases following surgery and might be an alternative neoadjuvant treatment in the future. A number of small preliminary trials have sown the possible potential of an immunotherapy approach however, larger clinical trials are needed.

In summary neoadjuvant chemotherapy and chemo-radiotherapy have both shown a significant benefit to survival of oesophageal cancer patients with resectable disease. Chemo-radiotherapy appears more effective, however, is associated with a higher postoperative mortality than preoperative chemotherapy. Further large scale randomised control trials using new chemotherapeutic agents are on the horizon and new treatments such as immunotherapy which have the ability to specifically target only malignant tissue may provide further improvement in survival in these patients.

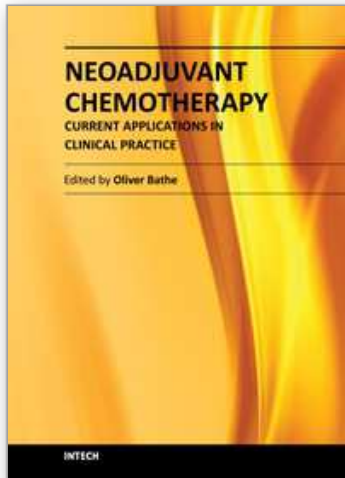
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The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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