Meta-Analysis on Recent Updates on Clinical Approach in Management of Carcinoma of Colon in Common Surgical Practice

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Published evidence suggests that in the very recent years, there is a tremendous revolution in the traditional concept and molecular basis of colorectal cancer, particularly colonic cancer. In general, colorectal cancer is considered to be the second most common cause of cancer death worldwide, a burning issue despite of conceptual advancement. With gene expression profile and with up-gradation of modalities of colonic surgery, battle lines are being drawn in this very complicated filed by the colorectal oncologist and surgeons. Although in spite of great emphasis, we still have drawback, no doubt. Quite reasonably, the main aim of this meta-analysis is to evaluate the different aspects of current advancement and up-gradation of this particular issue in relation to current evidence. In fact, this attempt is a conceptual triumph in the very complex gambling board of colonic cancer management in contrast to traditional thoughts.

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Key words: Meta-analysis, carcinoma, colon

Introduction

Having quite well established in meta-analysis of RCTs in recent few years, although along with rectum, colon cancers are the second most leading causes of all cancer death worldwide, it is an eminently curable disease, if diagnoses at an early stage, however it is a matter of great distress that most often the disease is only diagnosed at a very advanced stage usually after metastasis. So, this urgent to address and focus on some of the special aspects of management of colon cancer, on which the most latest research studies are centered around and the findings of these researches are quite impressive. The main aspect of this article is to highlight on such update findings on some unsettled issue in a nutshell on the very complex path of management of colon cancer.

Genetic Background

The development of colonic carcinoma is supposed to be the result of adenoma-carcinoma sequences most frequently due to multi-mutation of oncogenes or tumor suppressor genes. There is much evidence to support the model drawn by theadenoma-carcinoma sequences hypothesis[1, 2] (explanation box 1). About 18 specific genes have been already established for its mutative role for development of adenocarcinoma of colon and on the basic of gene one of latest advancement in this regard is the Gene Expression Profile[3,4]. Colon cancer

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pathological staging fails to accurately predict recurrence, and to date, no gene expression signature has proven reliable for prognosis stratification in clinical practice, perhaps because CC is a heterogeneous disease[3].

Evidence for adenoma-carcinoma sequences
✓ The prevalence of colonic adenoma & carcinoma is very similar except the carcinoma patients are about 5 years older
✓ The distribution of colonic carcinoma is same as adenoma
✓ Small carcinoma are almost always associated with adjacent adenomatous lesion
✓ Adenomas are found with about third of all colonic resection with carcinoma
✓ Sporadic adenomas are identical to the adenomas of FAP, which has a chance of 100% development of adenoma carcinoma unless treated
✓ Larger adenoma most likely to be associated with high grade dysplasia
✓ Incidence of colonic carcinoma falls with screening with colonoscopy & polypectomy

Explanation box 1: Hypothesis of adenoma-carcinoma sequences[1, 2]

Gene Expression Profile

Gene Expression Profiling is a very new avenue for the surgeons for the colonic cancer management. Adenocarcinomas of colon behave and response differently on the basis of mutations and therefore, their routes of management varies greatly. In other words, there is no common route at all[4, 5]. Moreover, in figure 1, it is clearly shown that the Therapeutic Index of adjuvant therapy is indeed very low.[6]

It is also well established that in a majority of cases, there is an inappropriate use of adjuvant therapy either by under or by over treatment, as there is no clinically effective tool which can predict precisely which patients will be befitted by adjuvant therapy and which are not. To resolve this problem, Gene Expression profile is that targeted clinical tool and of course, a remarkable milestone regarding this particular issue[7, 8] (summary box 2).

The concept of Fast-track surgery

Fast-track surgery or enhanced recovery after surgery (ERAS)/ enhanced recovery programme (ERP) is a multimodal comprehensive evidence based rehabilitation programme aimed at enhancing postoperative recovery and outcome by attenuated stress related organ dysfunctions& characterized by planned discharge after 48 hours in patients undertaking even major surgery[10,11,12,13]. (figure 3).

Benefits
Appropriate selection of option
Appropriate selection of candidate warrant neoadjuvent/adjuvant
Near precise prediction of prognosis & recurrence

Explanation Box 2. Benefit of Gene Expression Profile[9]

In different RCTs it is now acceptable that in case of ERP (Enhanced Recovery Programme, the average length of hospital staying is 2-3 days in contrast to conventional surgery where it is 10-14 days[1] (Figure 4).

Published evidence confirms the benefits of fast track surgery include the reduced hospitalization rate, lower morbidity, cost effectiveness, patient's satisfaction, safety etc[1,1]

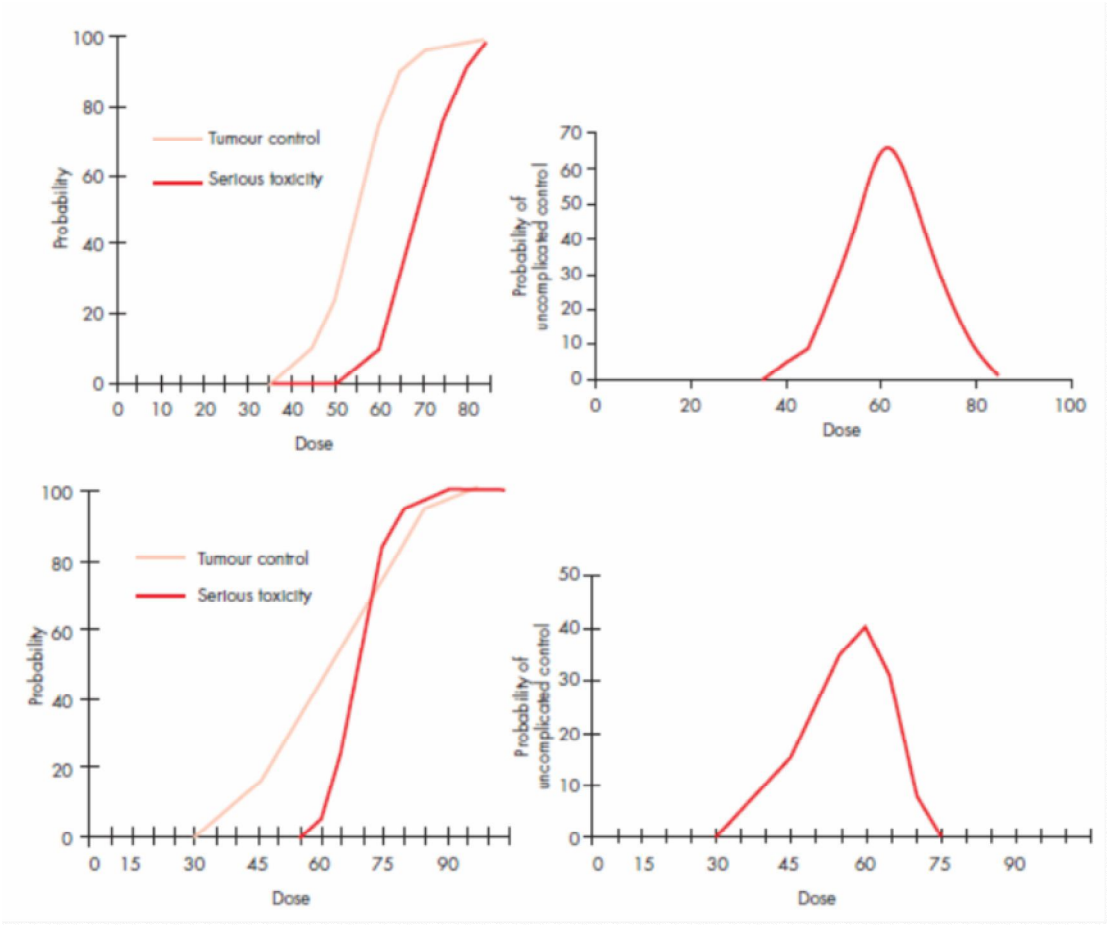

Figure 1. Relationship between dose, response and the probability of uncomplicated cure[6]

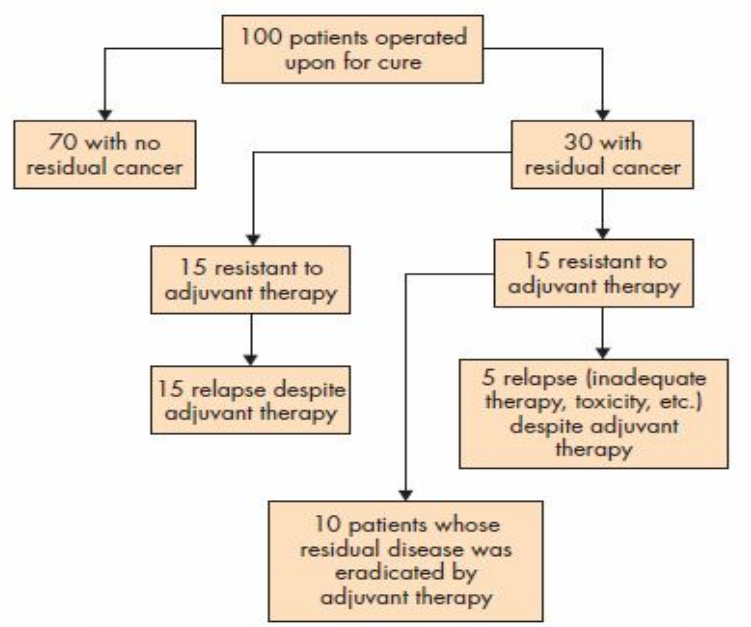

Figure 2. The concept of adjuvant therapy[6]

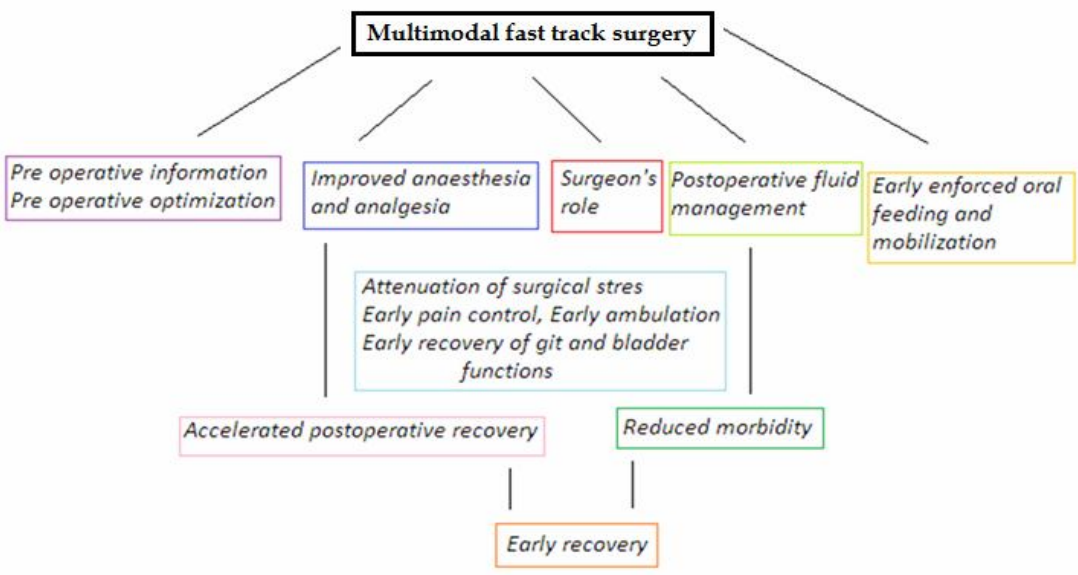

Figure 3. Essential component of Fast Track Surgery[1,14]

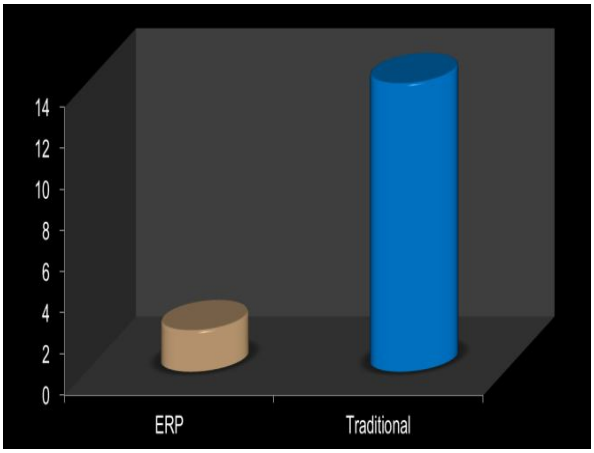

Figure 4. Average length of hospital staying

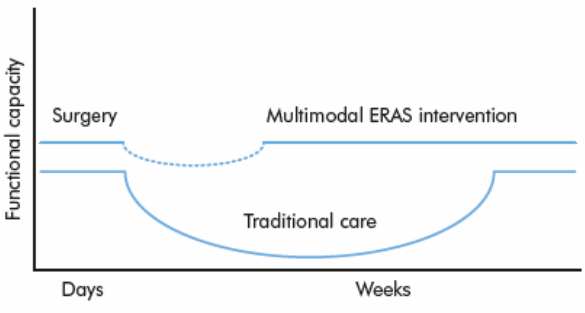

Figure 5. Enhanced recovery after surgery (ERAS)

It is important to understand that the discharge criteria in fast tract surgery in contrast to conventional surgery remain unaltered but achieved sooner by the essential components of ERAS/ERP[9] (figure 5).

The concept of dynamic pain relief of ERP

Analgesic options
o Pre-emptive analgesia
o Balanced analgesia
o Central axial block
Spinal analgesia Epidural analgesia
o Neuro-axial block
o Patient controlled analgesia

Explanation box 3. Dynamic pain control[14]

"Use of central blockade (spinal or epidural) with general anaesthesia versus general anaesthesia alone demonstrated significant reduction in postoperative mortality and morbidity including MI, pneumonia, thrombo-embolic complications, acute renal failure, and bleeding and transfusion requirement[14]"

"Epidural analgesia was safe and resulted in better pain relief during the 1st 3 POD and reduced pulmonary morbidity compared to other analgesic techniques[14]"

The concept of Pre-emptive analgesia

This implies the use of appropriate analgesia preoperatively to enhance the postoperative analgesic outcome by reducing the stress related catabolic response and therefore this is one of the main components of ERP.[13,14]

The concept of multimodal or balanced analgesia

Additive or synergistic effects by combinations of different analgesic agents (opioids, local anaesthetics, NSAIDs, COX 2 inhibitors, paracetamol) or techniques (peripheral nerve blocks, central neuroaxial block and patient controlled analgesia) and provides reduction of side effects owing to lower doses of the individual drugs[14].

Patient controlled analgesia

This is a system of delivery of intravenous opiate, the dose of which is controlled by patient himself. The patient can administer a bolus (usually of 1 ml in adult) by pressing the control button.A 5 min period during which the system will not response to a second request for a bolus is usually satisfactory[14].

Advanced treatment modalities

Table I: Advanced treatment modalities

Advanced modalities	Sub-Groups
❖ Targeted therapy: (FDA approved)	✚ Angiogenesis inhibitors ✚ TGF inhibitors ✚ Epidermal growth factor (EDGF) inhibitors ✚ Tyrosine kinase inhibitors
❖ Radio-embolization	
❖ Blood based DNA testing	
❖ Immunotherapy (Vaccination)	✚ Autologous dendritic cell derived

Targeted therapy

Angiogenesis inhibitors (Biological drugs)

These are the monoclonal antibodies that bind to the, epithelial receptor, inhibit angiogenesis and kill cancer cell as well as prevent cancer cell to spread. Brevacizumab, Avastine are the classical example of drug of this group[15].

Epidermal Growth Factor (EDGF) Inhibitors

These are also the monoclonal antibodies that bind to the, epidermal growth factor receptor and inhibit cancer. The associated drugs of this group are Cetuximab, Panitumumab etc[15].

Tyrosine Kinase Inhibitors

The recent drugs of this group are Erlotinib (Trceva), Strivarga (Regorafenib) etc.These are multi-kinase inhibitors which are highly effective especially in case recurrent & metastasis. A few months survival benefit has been observed[15].

The issue of complete clinical & pathological response

In a (15 to 30 percent) proportion of patients, who receive preoperative chemo-radiation for locally advanced (T3, T4, NX) colonic cancer achieve a complete response clinically and pathologically (confirmed by colonoscopy, biopsy & histopathology or excisional biopsy after surgery). Support is growing in the United Kingdom for the concept of "waiting to see" and not proceeding to radical surgery when a complete response is observed. When a complete response is observed, after definitive radical surgery, it is highly predicted that the chance of recurrence is indeed very low[16].

Table II: Chemoprevention for colon cancer

Substances	Sub-groups
NSAIDs	Aspirin Cyclo-oxygenase-2 (COX-2) inhibitors
Folic acid	
Calcium	
Vitamin D	

Chemoprevention of colonic cancer

Chemoprevention can lower the risk of cancer or slow its development. It is not used to treat cancer. To reverse, suppress, or prevent the development of colonic cancer, the use of natural, synthetic (made in a laboratory), or biologic (from a living source) substances are now being popularized (table II)[17].

Hormone-Replacement Therapy & chemoprevention

During the past 20 years, mortality from colorectal cancer has decreased slightly in men but much more in women[18]. A possible explanation for this difference is the increasing use of postmenopausal hormone-replacement therapy[19].Estrogens may prevent colorectal cancer by decreasing the production of secondary bile acids, by decreasing the production of insulin-like growth factor I, by exerting direct effects on the colorectal epithelium, or by a combination of these mechanisms.

Conclusion

Despite of huge advancement of recent manage strategy of colonic cancer, surgical resection still remains the only curative hope, and the likelihood of cure is greater when the disease is detected at an earlier pathological stage. Early detection is the goal of screening programs that use periodic examination of stool for occult blood, with or without intermittent endoscopic examination of the bowel. Nevertheless, the optimal method for early detection remains uncertain, and despite widely published recommendations for such screening programs, compliance still remains very poor.

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