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Tumor Markers of Neo-Adjuvant Chemo-Radiation Response in Rectal Cancer

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1. Introduction

Radiation therapy alone or in combination with chemotherapy has lead to improved outcomes in the management of rectal cancer patients. Many studies have demonstrated that for locally advanced rectal cancer, preoperative chemoradiation (CRT) significantly improves local control, reduces toxicity profiles and the risk of disease recurrence (Habr-Gama, Perez et al. 2004), (Kapiteijn, Marijnen et al. 2001), (Frileux, Burdy et al. 2007), (Horisberger, Hofheinz et al. 2008), (Krook, Moertel et al. 1991), (Sauer, Becker et al. 2004). Highly radiosensitive cancers completely regress, leading to improved survival. A histology tumor grading system is used to determine the success of radiation prior to surgery. This is called a tumor regression grade (TRG). Originally described for oesophageal tumors, the TRG system has been adapted to rectal cancer (Mandard, Dalibard et al. 1994). Regression grading stratifies response based on the biological effect of radiation on tumors, dividing it into five different grades based on the ratio of fibrosis to tumor where TRG1: no residual cancer; TRG2: rare residual cancer cells; TRG3 fibrosis outgrowing residual cancer; TRG4: residual cancer outgrowing fibrosis and TRG 5: absence of regressive changes. This TRG scoring system is extremely valuable as it can highlight those tumors demonstrating large variation in biological response to radiation not undergoing a T stage change (Bouzourene, Bosman et al. 2002). In a paper by Ryan et al, they have revised the 5 point TRG system into a 3 point where grade 1 indicates a complete response, grade 2 a partial response and grade 3 no response (Ryan, Gibbons et al. 2005). Currently, only approximately 25% of patients who receive CRT treatment obtain a complete pathological response (Valentini, Coco et al. 2002; Sauer, Becker et al. 2004). Disease free survival in these patients is improved with a reduce rate of local recurrence However, up to 75% of patients receive a treatment that achieves little or no benefit and an increased risk of second cancers has been documented within or adjacent to the irradiated volume (Birgisson, Pahlman et al. 2005).

The broad and unpredictable response to tumor of patients with rectal cancer treated with preoperative chemoradiotherapeutic interventions shows that our understanding of the molecular events leading to radioresistance in patients affected with this malignancy is limited. This variation is thought to depend on tumor size but also on the biological properties of individual tumors. It is important to understand what factors within the tumor predict high sensitivity to the new-adjuvant regimen and what determines resistance, as this information may allow tailor-made individualization of therapy. Classification of

responders and non responders may also spare poorly responding patients from undergoing treatment which would derive no benefit for them. In contrast, the ability to predict good response may alter the subsequent management of patients. Many studies have examined prognostic and predictive molecular marker expressions in rectal cancer treated with neo-adjuvant radio-chemotherapy. However, some of these studies only examined expression profiles in the tumor excised after surgery (Bertolini, Bengala et al. 2007). In this chapter, we will critically review the assessed predictors of histological response to new-adjuvant radiation for rectal cancer patients. There are many studies in the literature which have compared biomarker expression levels before and after new-adjuvant treatment and correlated expression differences with a measure of patient outcome. These studies however are not as useful in prospectively predicting which patients will respond to new-adjuvant therapy and are not discussed in this review.

Studies utilizing molecular response predictors from archival pre-treatment tumor tissues have identified several promising predictive markers including p21, thymidylate synthase expression, EFGF status, apoptosis markers and p53 gene status. Global gene expression studies have also been performed. We will discuss these and others in relation to their ability to predict response and resistance to new-adjuvant treatment for rectal cancer patients. A number of listed biomarkers above will be discussed in detail in relation to their potential to predict response. A number of these factors can interact together at different cellular levels (Figure 1).

In figure 1, p53 can induce apoptosis, growth arrest and or senescence. Activation of p53 can induce expression or activation of pro-apoptotic Bcl2 family proteins (eg: Bax, Puma and Noxa) that coverge on the mitochondria and induce cytochrome c release. In the cytosol, cytochrome c binds Apaf1 which activates caspase 9 which activates caspase 3. It is also proposed that p53 can impair mitochondrial function. The p53 mediated mitochondrial dysfunction triggers a cycle of DNA damage, p53 activation, a compromised mitochondria and increased ROS levels leading to additional DNA damage.

2. Biomarker analyses

2.1 p21

The p21 protein is transcriptionally activated by p53 in response to DNA damage (el-Deiry, Kern et al. 1992). This causes the cells to arrest in G1 through the alteration of cyclin dependent kinases. It has been studied as a response predictor as disruption of the cell cycle networks may be a causative factor of radioresistance (Waldman, Kinzler et al. 1995), (Brugarolas, Chandrasekaran et al. 1995). Loss of wild type p21 or the presence of mutated p21 can radiosensitise cancer cells (Lu, Yamagishi et al. 1998), (Waldman, Lengauer et al. 1996), (Wang, Elson et al. 1997), (Tian and Quaroni 1999). On the basis of in vitro studies, it is predicted that tumors with low or absent p21 expression would be more sensitive to radio/and chemotherapy, ultimately leading to improved patient outcome. The levels of p21 expression have been investigated in a small number of immunohistochemistry based studies, some of which demonstrated some association with response (Reerink, Karrenbeld et al. 2004), (Fu, Tominaga et al. 1998; Qiu, Sirivongs et al. 2000). Some of these studies showed that positive p21 tumors were associated with poor survival (Reerink, Karrenbeld et al. 2004; Bertolini, Bengala et al. 2007). Four year overall survival rates in biopsies with high p21 expression levels was 43% compared with 83% 4 year survival in biopsies with low p21 expression levels (Bertolini, Bengala et al. 2007). However, others have shown no correlation

between p21 expression levels and pathologic response (Rau, Sturm et al. 2003). The inclusion of p21 screening is warranted, as the referenced studies in table 1 below had low case numbers and results between centers did not show good reproducibility.

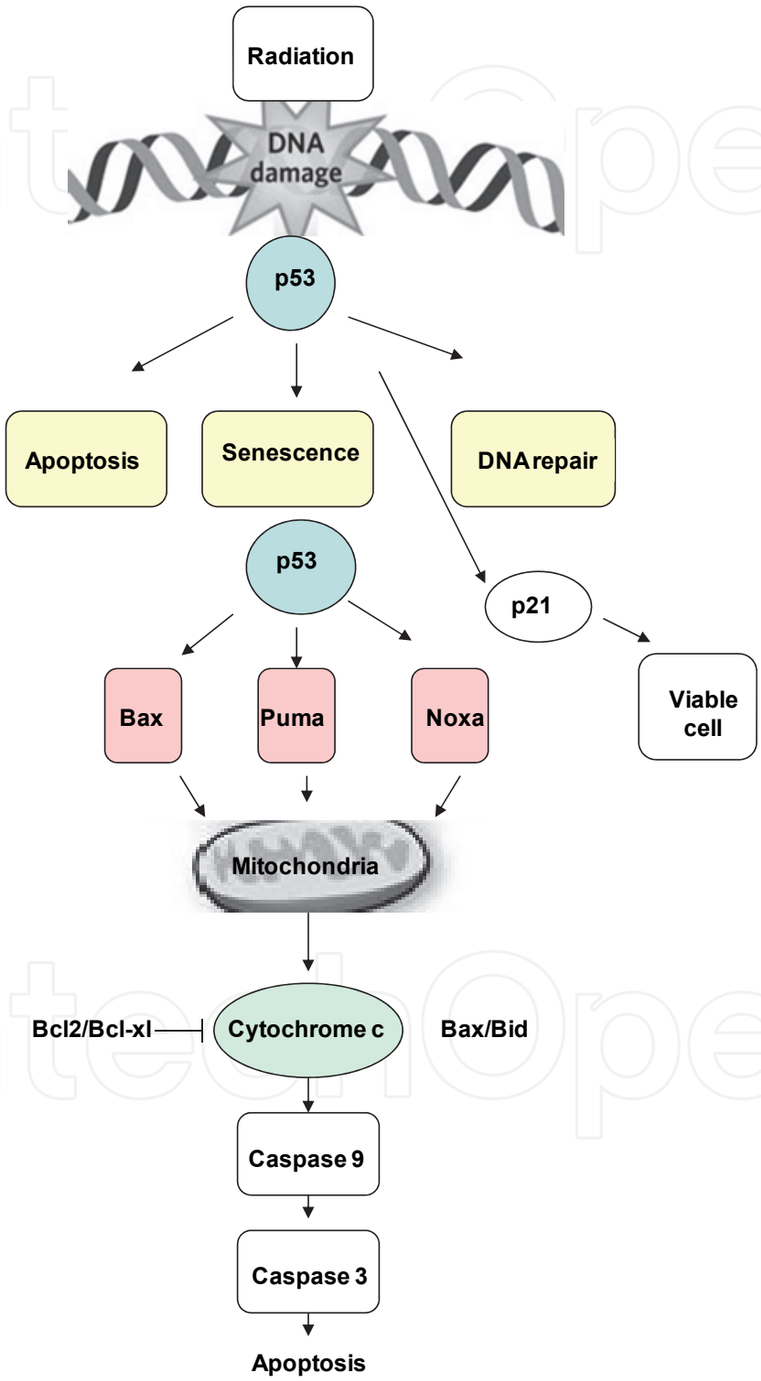

Fig. 1. p53 interaction with p21, DNA repair and mitochondrial dysfunction

Author	Technique	Study Outcome
Bertolini *et al*	IHC	Low p21 correlates with improved survival
Rau *et al*	IHC	Low p21 correlates with non responders
Charara *et al*	IHC	P21 positive tumors detected in responders
Reerink *et al*	IHC	High p21 correlates with poor survival
Kudrimoti *et al*	IHC	No correlation
Negri *et al*	IHC	No correlation
Lin *et al*	IHC	No correlation
Chang *et al*	IHC	No correlation

Table 1. Studies assessing p21 and Patient Outcome

2.2 Thymidylate synthase

Thymidylate synthase (TS) plays a crucial role in DNA synthesis. It is a primary target of 5-fluorouracil (5-FU) in the treatment of colorectal cancer. Overexpression of TS is associated with 5FU resistance and overall poor patient outcome (Salonga, Danenberg et al. 2000), (Lenz, Danenberg et al. 1998). Numerous studies assessing TS expression have found that pretreatment biopsies negative for TS were predictive of response (Saw, Morgan et al. 2003), (Diez, Ramos et al. 2003), (Jakob, Liersch et al. 2008), (Negri, Campanini et al. 2008). 3 studies revealed a better outcome with low or absent pretreatment TYMS expression, however another study demonstrated better outcome with high TYMS expression. It must be noted that the studies that did show a strong correlation between high pretreatment TYMS and outcome were performed on very small patient numbers. Therefore, the use of TYMS IHC screening is not recommended based on these small pilot studies performed. Evaluation of the TYMS allele has also been examined which determines the number of tandem repeats in the TYMS gene promoter region (Spindler, Nielsen et al. 2007), (Horie, Aiba et al. 1995), (Kawakami, Salonga et al. 2001) (44, 52,53). Villafranca et al has shown that patients homozygous for the triple repeat showed 22% downstaging compared to 60% downstaging in patients either homozygous for the double repeat (Horie, Aiba et al. 1995). TYMS DNA analyses may be valuable as a predictive biomarker, however its clinical utility needs to be evaluated in larger multi-center studies.

2.3 P53

P53 is known to play a role in apoptosis and in regulating sensitivity of tumors to radiation and chemotherapy (Bunz, Hwang et al. 1999), (Bunz, Dutriaux et al. 1998), (Kuerbitz, Plunkett et al. 1992), (Lowe, Schmitt et al. 1993), (Lowe, Ruley et al. 1993). For this reason, p53 is the most studied response predictor in rectal cancer with to date 22 different studies examining its potential to predict response to new-adjuvant treatment for rectal cancer patients. Assessment of p53 status has been performed by many different techniques

including immunohistochemistry, polymorphism screening and direct gene sequencing (Reerink, Karrenbeld et al. 2004), (Rebischung, Gerard et al. 2002), (Kandioler, Zwrtek et al. 2002), (Qiu, Sirivongs et al. 2000), (Fu, Tominaga et al. 1998), (Rodel, Grabenbauer et al. 2002), (Abe, Sakaguchi et al. 2001), (Sakakura, Koide et al. 1998), (Luna-Perez, Arriola et al. 1998), (Komuro, Watanabe et al. 2003), (Spitz, Giacco et al. 1997), (Elsaleh, Robbins et al. 2000), (Saw, Morgan et al. 2003), (Scott, Hale et al. 1998), (Okonkwo, Musunuri et al. 2001), (Tannapfel, Nusslein et al. 1998), (Kim, Park et al. 2001), (Spitz, Giacco et al. 1997). The majority of work has been IHC based studies. Of these, only 18% of studies could be used to significantly predict response (Fu, Tominaga et al. 1998), (Spitz, Giacco et al. 1997; Komuro, Watanabe et al. 2003). These showed that pretreatment biopsies negative for p53 were predictive of complete tumor regression. The remaining 82% of studies did not show a positive association with levels of p53 expresison and treatment response. Some of the biggest studies were performed by Chang et al, and Bertolini et al and these revealed no correlation between mutant p53 expression and treatment outcome (Chang, Jung et al. 2005), (Bertolini, Bengala et al. 2007). Direct sequencing of the p53 gene (exons 2-10) revealed mutant p53 genotype was significantly associated with radioresistance (Rebischung, Gerard et al. 2002), (Kandioler, Zwrtek et al. 2002). These 2 studies revealed similar results however, the number of independent groups validating these results are limited. Overall, the majority of studies revealed no correlation between p53 and treatment outcome, suggesting that p53 is unlikely to serve as a predictor of response to new-adjuvant CRT.

Author	Technique	Study Outcome
Negri *et al*	IHC	High TYMS correlates with high rate of response
Saw *et al*	IHC	Lack of TYMS correlates with T stage downstaging
Bertolini *et al*	IHC	No correlation
Okonkuro *et al*	IHC	No correlation
Jakob *et al*	PCR	Low TYMS correlates with increased TRG stage
Stoehlmacher *et al*	PCR	Non significant
Spindler *et al*	PCR	TYMS2/2 levels correlate with increased TRG stage
Willafranca *et al*	PCR	TYMS2/2 levels correlate with increased TRG stage
Terrazzino *et al*	PCR	TYMS2/2 levels correlate with increased TRG stage

Table 2. Studies assessing Thymidylate Synthese and Patient Outcome

Author	Technique	Study Outcome
Jakob *et al*	IHC	No correlation
Kim *et al*	IHC	No correlation
Okonkuo *et al*	IHC	No correlation
Scott *et al*	IHC	No correlation
Kudnmoti *et al*	IHC	No correlation
Luna Perez *et al*	IHC	Positive p53 correlated with less tumor regression
Reerink *et al*	IHC	No correlation
Terzi *et al*	IHC	No correlation
Esposito *et al*	IHC	Positive p53 correlated with more tumor regression
Spitz *et al*	IHC	Positive p53 correlated with less tumor regression
Rodel *et al*	IHC	No correlation
Rau *et al*	IHC	No correlation
Lin *et al*	IHC	Negative p53 correlated with higher rate of response
Diez *et al*	IHC	No correlation
Terrazzino *et al*	IHC	No correlation
Bertolini *et al*	IHC	No correlation
Chang *et al*	IHC	No correlation

Table 3. Studies assessing p53 and Patient Outcome

2.4 Epidermal growth factor receptor (EGFR)

EGFR regulates many different cellular processes including cell proliferation, differentiation and apoptosis. It is overexpressed in 50-70% of cancers and is associated with more advanced tumor staging, poor prognosis and radiation resistance. (Akimoto, Hunter et al. 1999), (Liang, Ang et al. 2003). It has also been used as a therapeutic target with the development of new molecular targeted therapies such as Cetuximab (Eribitux) (You and Chen), (Liu, Guo et al.), (Liao, Sun et al.). There is very limited evidence on this receptor in relation to response to radiation in rectal cancer patients (Giralt, de las Heras et al. 2005), (Li, Kim et al. 2006), (Spindler, Nielsen et al. 2006), (Spindler, Nielsen et al. 2007). One study has shown an association between high EGFR levels and poor survival (Liu, Guo et al.). In tumors showing more than 50% positivity correlated with a shorter disease free survival. Multivariate analysis demonstrated low EGFR expression was a predictive factor for tumor downstaging (Liu, Guo et al.). The debate for screening EGFR levels is very weak and tenuous.

Author	Technique	Study Outcome
Spindler *et al*	IHC	No correlation
Spindler *et al*	PCR	EGFA61G SNP + EGFRSp1 with TYMS2/2 predicts Increased tumor regression
Giralt *et al*	IHC	No correlation
Bertolini *et al*	IHC	No correlation
Kim *et al*	IHC	No correlation

Table 4. Studies assessing EGFR and Patient Outcome

2.5 Ki67 and Cox2

Ki67 is required for cell cycle control (Scholzen and Gerdes 2000), (Schluter, Duchrow et al. 1993), (Linden, Ma et al. 1993). While it has been used as a prognostic factor for colorectal cancer, results have been inconclusive (Ogata, Greca et al.), (Guzinska-Ustymowicz, Pryczynicz et al. 2009), (Santagostino, Saggia et al. 2007). A small number of independent studies have examined the levels of Ki67 positivity in pretreatment biopsies from rectal cancer patients (Kudrimoti, Lee et al. 2007), (Debucquoy, Goethals et al. 2006), (Tannapfel, Nusslein et al. 1998), (Reerink, Karrenbeld et al. 2004), (Rodel, Grabenbauer et al. 2002), (Charara, Edmonston et al. 2004), Some studies have shown a positive association with Ki67 index higher in responders compared to non responders (Kim, Park et al. 2001; Jakob, Liersch et al. 2008). The remaining studies showed no correlation between Ki67 status and patient outcome. In the small number of studies that did show a positive correlation between Ki67 and response, these were conducted on a very small patient cohort. It appears unlikely that measurement of the proliferation status in pretreatment biopsies will be clinically useful.

Another molecule known to promote tumor growth is Cox 2. Cox 2 catalyses the conversion of arachidonic acid to protaglandins, especially PGE2. COX2 inhibition in conjunction with radiation can significantly enhance tumor response by blocking prostaglandin release (Kishi, Petersen et al. 2000). In laryngeal (Nix, Lind et al. 2004) and cervical cancers (Kim, Kim et al. 2004), (Kim, Kim et al. 2002), COX 2 expression in pre treatment biopsies may be indicative of treatment response to CRT. Cox2 has been evaluated in pre rectal biopsies (Watwe, Javle et al. 2005), (Kobayashi, Hashiguchi et al. 2007), (de Heer, Gosens et al. 2007), (Giralt, Navalpotro et al. 2006), (Min, Choi et al. 2008), (Smith, Reynolds et al. 2006). And its overexpression was significantly associated with poor response to treatment, suggesting that COX2 may mediate radioresponsiveness. However, study numbers are small and no multi-centre studies to validate these findings have been reported to date.

2.6 Mitochondrial proteins bcl2/bax

Bcl2 and Bax regulate caspase activation and this activation can regulate apoptosis in many disease states (Teijido and Dejean), (Thees, Hubbard et al. 2005), (Brambilla, Negoescu et al. 1996). Bcl2 and Bax are prosurvival and proapoptotic proteins respectively. Bcl2 maintains mitochondrial outer membrane integrity (Teijido and Dejean ; Luo, Budihardjo et al. 1998;

Zhang, Holzgreve et al. 2001). Bax can be activated by pro apoptotic stimuli or p53 and expression can be altered following radiation and is associated with resistance to chemotherapy (Miguel, Wajsenzon et al. 2007), (Przemeck, Duckworth et al. 2007), (Murphy, Mabruk et al. 2002), (Johnson, Xiang et al. 1998; Butt, Firth et al. 2000), (Strobel, Swanson et al. 1997), (Khanna, Wie et al. 1996). This is in contrast to overexpression of bcl2 is associated with chemotherapy resistance and protects cells from radiation induced apoptosis (Hahn, Lai et al. 2003), (Vrana, Grant et al. 1999). 12 studies have assessed these proteins, 8 for Bcl2 expression and 4 have evaluated Bax expression as predictive markers (Qiu, Sirivongs et al. 2000), (Rodel, Grabenbauer et al. 2002), (Rodel, Hoffmann et al. 2002), (Scott, Hale et al. 1998), (Okonkwo, Musunuri et al. 2001). Only one study has found that Bcl2 was an indicator of response in pre treatment biopsies, where 60% of complete responders were bcl2 positive in pretreatment biopsies compared to 16% bcl2 positive in the partial responders. One of the Bax studies showed a significant correlation between higher Bax expression in biopsies associated with treatment response. Overall, these markers do not prove useful as significant markers of response to new-adjuvant CRT.

Author	**Technique**	**Study Outcome**
Kudrimoti *et al*	IHC	Positive bcl2 expression correlates with complete response
Chang *et al*	IHC	Bax expression correlates with increases tumor regression
Scott *et al*	IHC	No correlation
Okonkwo *et al*	IHC	No correlation
Reerink *et al*	PCR	No correlation
Tannapfel *et al*	IHC	No correlation
Charara *et al*	IHC	No correlation
Rodel et al	IHC	No correlation

Table 5. Studies assessing bcl2/bax and Patient Outcome

2.7 Microsatellite instability, mis match repair and hypoxia

Evaluation of the levels of DNA repair in pretreatment biopsies may be important in predicting response or resistance to CRT. Tumors which show microsatellite instability usually have a better prognosis and have altered response to radiotherapy compared to tumors with an intact repair system (Peltomaki 2003). This effect has been evaluated in a small number of clinical trials, however screening for MSI status and presence or absence of the mis match repair proteins did not correlation with treatment response (Qiu, Sirivongs et al. 2000), (Charara, Edmonston et al. 2004), (Rau, Sturm et al. 2003) . However, assessment of

Ku70, a protein involved in double strand break repairs (Ayene, Ford et al. 2005) could predict response when combined mutant p53 status (Komuro, Watanabe et al. 2003). Markers of tumor hypoxia have also been assessed as a response predictor in rectal cancer. Qui et al have found that histological response was not correlated to VEGF expression levels in pretreatment biopsies (Qiu, Sirivongs et al. 2000). Other studies combined VEGF expression levels in serum/plasma with serial dynamic contrast-enhanced (DCE) MRI, a marker of vessel permeability. While again VEGF levels did not correlate with treatment response, higher permeability on DCE MRI significantly correlated with better response to CRT (George, Dzik-Jurasz et al. 2001).

2.8 Microarray and proteomic studies

While targeted-therapies use single marker approaches, tumor response to CRT is complex and unlikely to be attributed to one factor alone. Transcriptional profiling of tumors has shown considerable promise as a predictive approach to treatment, with commercially available microarray profiling platforms, MammaPrint and OncoTypeDX, already in place for breast cancer prognostics (van 't Veer, Dai et al. 2002; Paik, Shak et al. 2004). This has provided support for predictive genomics research in other cancer types, including rectal cancer. A number of studies carried out in recent years have aimed to identify gene and/or protein signatures predictive of response to CRT in rectal cancer. Prior to the development of genomic and proteomic screening studies, assessment of predictive markers suggested that *p53*, *Bcl2*, *Bax*, and microsatellite instability are of no predictive value as discussed above.

Ghadimi *et al.* were among the first to use gene expression profiling with the aim of predicting response to new-adjuvant CRT in rectal cancer (Ghadimi, Grade et al. 2005). A significant difference in gene expression was identified between responders and non-responders for 54 genes, while the ability of this gene profile to predict response was validated in 83% of patients (78% sensitivity, 86% specificity). While this is a promising observation, the authors noted that validation of these findings in large, independent studies would be required. Watanabe *et al.* also carried out DNA microarray analysis of gene expression profiles in response to new-adjuvant radiotherapy in rectal cancer (Watanabe, Komuro et al. 2006). They identified 33 genes with a significant difference in expression between responders and non-responders (82.4% accuracy).

While expression of pro-apoptotic genes was higher in responders, anti-apoptotic gene expression was higher in non-responders. A later study carried out gene microarray analysis on tumor tissues from 46 patients with rectal cancer, with response to CRT evaluated using Dworaks tumor regression grade. From a gene-set comprising the top-ranked 95 genes demonstrating altered expression (between partial and complete-response), response to CRT was accurately predicted in 84% of training samples and 87% of validation samples (Kim, Lim et al. 2007). Using 43 biopsy specimens from patients with locally advanced rectal adenocarcinoma, a 43-gene expression signature of response was identified by Rimkus *et al* (Rimkus, Friederichs et al. 2008). These genes mainly encoded proteins involved in nuclear processes, associated with transport function, or implicated in apoptosis regulation (caspase-1), supporting previous observations (Watanabe, Komuro et al. 2006). A subsequent small study of rectal cancer patients who underwent preoperative CRT (n=17) revealed seventeen genes with significantly altered gene expression levels. These included apoptosis, metalloproteinase, transforming growth factor beta-1, DNA repair, and cell

proliferation-related genes (Nishioka, Shimada et al.). The activity of certain subsets of kinase signaling pathways has also been proposed to predict response to CRT in rectal cancer. A microarray study of 67 patients with advanced stage rectal cancer suggested that multiplex kinase activity profiling may identify biomarkers to predict tumor response to CRT, with several discriminating phosphosubstrates representing proteins derived from signaling pathways implicated in radioresistance (Folkvord, Flatmark et al.).

Using a panel of 48 cancer cell lines, a 10-gene signature of radiosensitivity was identified and used as a predictor of an intrinsic radiosensitivity index (RSI). This was applied to a rectal cancer cohort, which was treated with concurrent chemoradiation. The predicted RSI was significantly different in responders versus non-responders. This effect was also observed in head-and-neck and oesophageal cancer cohorts, a combined total of 118 patients and the first systems-based radiosensitivity model to be validated in multiple datasets (Eschrich, Pramana et al. 2009). A subsequent study used 12 colorectal cancer cell lines to examine response to CRT. The authors identified many genes involved in the MAP-kinase pathway or cell cycle genes, and suggested that both insulin and Wnt signaling pathways may have relevance for treatment response.

A recent study was carried out to examine expression profiles from pretreatment biopsies for 51 rectal cancer patients. However, the classifiers obtained from this study did not have high sensitivity/specificity, with those with highest sensitivity having poor specificity and vice versa. Validation of these classifiers with previously published data was also difficult, prompting the authors to suggest that microarray analysis is not a valuable tool for predictive studies in rectal cancer (Brettingham-Moore, Duong et al.). Alternatives approaches should therefore also be considered for future predictive studies in rectal cancer.

Author	**Technique**	**Study Outcome**
Ghadimi *et al*	DNA Microarray	54 gene panel predicts response (78% sensitivity and 86% specificity
Watanabe *et al*	DNA Microarray	33 gene panel predicts response (82% accuracy)
Kim *et al* Okonkwo *et al*	DNA Microarray	95 gene signature predicts response (87% validation)
Allal *et al*	Proteomics	Differential expression of proteins between responders and non responders. Protein targets: Tropomodulin, heat shock 42, keratin 1 and notch2

Table 6. Studies assessing array profiles and patient outcome

A small number of studies have used proteomic approaches to identify a protein signature which can predict response to CRT. The earliest of these used 2D genes and subsequent

mass spectrometry to identify a small number of proteins which correlated with treatment response. These included tropomodulin, heat shock protein 42, keratin type 1 and notch-2 protein homolog. A number of these proteins are known to be associated with radioresistance (Allal, Kahne et al. 2004). The use of an integrated microarray and proteomics approach to predict response of patients on cetuximab demonstrated an enhanced predictive power, with 5 genes and 10 proteins predicting rectal cancer regression grade with 91.7% accuracy, 96.2% sensitivity and 80% specificity (Daemen, Gevaert et al. 2008). A similar approach was later taken by Debucquay *et al.,* who found that 16 genes were significantly altered following microarray analysis (Debucquoy, Haustermans et al. 2009). A decrease in proliferation gene expression was confirmed by IHC for Ki67 and further supported by an increase in TGFα in plasma samples from rectal cancer patients.

3. Concluding remarks

The relationship between biomarker expression and histological response to CRT has been investigated in a large number of studies. The vast majority of these studies have assessed single or multiple pre defined markers in small cohorts of patients. However, through these studies, a limited number of promising markers have been identified including TS expression, increased p21 and EGFR expression levels. While these markers have been assessed and have shown some promise, due to the limited number of studies assessing each marker using the same protocol, no marker to date can be considered as a clinical biomarker. The biggest problem with the studies has been the lack of statistical power. Assessment of these markers should be prospectively evaluated to elucidate their role as measures of predictive outcome, however it is unlikely that any single factor will determine response so a more global approach maybe more advantageous. The development of novel therapeutic targets for rectal cancer maybe greatly aided by the generation of global gene and protein expression profiles for responders and non-responders through microarray and proteomic studies. However, this will only be made possible by the use of large cross-institutional studies.

The discovery of specific biomarkers that could potentially predict a tumor response to treatment could prevent the above mentioned unfavorable consequence while focusing on patients that will benefit from new-adjuvant treatment. A successful biomarker(s) should predict responders versus non responders with high sensitivity and specificity levels. This biomarker should be validated prospectively in different patient cohorts from multi centre hospitals. Importantly, to conduct these prospective studies, it is vital that there is limited variation in the dose and duration of radiation, inclusion or type of chemotherapy given and pathological endpoints assessed. Another caveat is in relation to the collection and analysis. It is unknown whether the endoscopy biopsy truly reflects the biology of the tumor as a whole. Also, variability in IHC scoring systems could alter study outcomes. To date, these issues may contribute to conflicting results for the potential biomarkers as discussed in this chapter. In conclusion, the response of rectal adenocarcinoma to neo-adjuvant chemo-radiotherapy is limited to a defined group of patients. It is hoped in the future that the therapeutic course will be tailored to each patient based on analyses of initial pre treatment biopsy assessment, thus minimizing unnecessary treatment for rectal cancer patients. The next investigative step would be to conduct, initially, phase II trials prospectively to validate the predictive power of the most promising predictive markers and eventually phase III

prospective trials to separate categories of patients based on the likelihood of tumor response according to expression of the different molecules.

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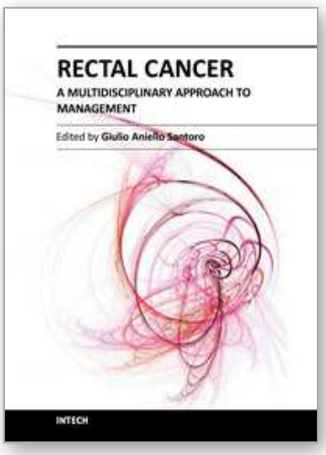

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Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

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