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Pathologic Complete Response in Rectal Cancer Patients After Neoadjuvant Chemoradiotherapy at the Philippine General Hospital

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Objective: The study aimed to document the pathologic complete response (pCR) rates at the Philippine General Hospital (PGH) from 2005 to 2009. The response to neoadjuvant chemoradiotherapy as evidenced by tumor downstaging was also documented.

Methods: The study included all adult patients with low to mid rectal tumors, described as tumors with distal extent 11 cm or below from the anal verge (FAV), who underwent resection after having undergone preoperative chemoradiotherapy. Patients who underwent surgery from January 1, 2005 to December 31, 2011 were included. Data pertinent to response to neoadjuvant chemoradiotherapy were collected. Frequencies and rates pertaining, particularly those relating to pCR and tumor downstaging, were computed.

Results: There were a total of 204 rectal resections for cancer over a seven-year period. The patients' mean age was 52.7 years (range: 22 to 83). There were 168 males and 136 females (ratio 1.2:1). Fifty-three percent of patients presented with clinical Stage IIIB. One hundred fifty five (41%) patients underwent either preoperative radiotherapy (14.15%, n=43) or combined chemoradiotherapy (36.82%, n=112). Of those who underwent long course chemoradiotherapy (LCCRT), 60.7 percent of tumors were downstaged. Twenty-one percent of tumors had a pCR. Among patients with a pCR, the mean age was 47.22 years (range 23-72 years). The average distance FAV was 5.7 cm (range 3-10 cm). Majority presented with clinical stage IIIB (66.7%), and nearly all (95.8%) underwent a sphincter-saving operation.

Conclusion: The utilization of neoadjuvant chemoradiation in our setting has shown comparable outcomes to those reported in foreign literature on rates of downstaging and pCR. A more protracted study should be pursued to assess for long-term outcomes regarding recurrence and survival.

Key words: rectal cancer, pathologic response, combined modality therapy

The management of rectal cancer has seen significant improvements, not only in surgical technique, but in forms of adjuvant therapy as well. Radiation therapy as an adjunct to surgery was commonly used in the post-operative setting.[1] Its value in the preoperative period, however, was confirmed with the publication of the results of the Swedish Rectal Cancer Trial on the outcomes of resectable rectal cancer after preoperative radiotherapy.[2]

The addition of chemotherapy to preoperative radiotherapy, on the other hand, has shown increased tumoricidal activity with evidence of downsizing and downstaging of lesions.[3] Such an approach expectedly increases survival, decreases symptomatic pelvic recurrence, allows for sphincter-saving surgery and reduces the long-term morbidity associated with post-operative radiation.[4-5] The use of neoadjuvant chemoradiation is particularly important for patients presenting with locally-advanced, unresectable rectal cancer, as the disease of the majority will be rendered resectable.[5] Moreover, chemoradiation delivered preoperatively is associated with less toxicity rates as compared to postoperative treatment.[6]

Pathologic complete response (pCR) is the desired outcome in pathologic analysis signifying no viable tumor. Patients who achieve a pCR after preoperative combined-modality therapy are significantly more likely to have a sphincter-preserving rectal resection and

higher recurrence-free and over-all survival rates.[7] Internationally, neoadjuvant chemoradiotherapy regimens are associated with a pCR rate of approximately 4 to 33 percent.[8-9]

In the Philippines, few centers offer neoadjuvant chemoradiotherapy to patients with rectal cancer. Most rectal cancer patients, therefore, end up with outright surgery and postoperative chemoradiotherapy. Thus, no data on pCR are available in the Philippine literature.

This study aimed to document the number and frequency of pathologic complete responders and rate of tumor downstaging after neoadjuvant chemoradiotherapy at the Philippine General Hospital.

Methods

The Integrated Surgical Information System (ISIS) of the Department of Surgery was used to track patients who were admitted and underwent resection for rectal cancer 11 cm or less FAV from January 1, 2005 to December 31, 2011. The search terms "rectal carcinoma", "rectal cancer" and "rectal CA" were used. Data from ISIS were supplemented with information from the patients' hospital records. Upon review of the available data, the patients who underwent preoperative long course chemoradiation were identified. A Data Collection Form was filled out. Frequencies and rates were calculated.

The UP-PGH Colorectal Cancer and Polyp Study Group has been managing rectal cancer patients through a multidisciplinary team approach since its formation in 2007.

All patients with a histologically-proven diagnosis of adenocarcinoma of the rectum are individually discussed at bimonthly conferences and the most appropriate treatment with consideration to financial and logistic limitations is provided the patient. Of utmost importance in the multidisciplinary approach is accurate clinical staging, as this will dictate the selection of patients who are indicated to receive neoadjuvant treatment. The authors routinely utilize the following available diagnostic modalities in arriving at a pre-treatment stage.

1. Abdominopelvic computed tomography (CT) scan with intravenous, oral and rectal contrast. The Group relies rely largely on a triple contrast abdominopelvic CT scan in determining the TNM stage of patients. A CT scan will provide information for possible adjacent organ involvement (T4). Circumferential tumor involvement (which may also be determined during physical examination and endoscopy) may indicate a T3 lesion. With endorectal ultrasonography (ERUS) and magnetic resonance imaging (MRI) not readily available to assist us in determining the depth of invasion, the Group relies on institutional data that have shown that 80 percent of patients with circumferential involvement have tumor stage of at least T3.

   Pararectal stranding, although non-specific, marks an area of inflammation. With the background of malignancy, the Group assumes that the pararectal stranding is due to lymph node involvement (N+).

   Finally, a CT scan will assist them in determining the presence of metastatic disease within the abdomen (e.g. liver metastasis, carcinomatosis).

2. Colonoscopy: A complete colonoscopy is performed to rule out the presence of synchronous lesions. Furthermore, inability to insert the scope past tumor is an indication in PGH to perform pretreatment fecal diversion.

3. Rigid proctosigmoidoscopy: Tumor height is determined most accurately with the use of a rigid proctoscope. This is important in determining if the lesion is "colon" (> 12 cm FAV) or "rectal" (≤ 12 cm FAV), and will dictate the eventual management.

4. Chest radiograph (CXR): Ideally, a chest CT scan is recommended to rule out pulmonary metastatic involvement. However, financial limitations usually hinder the Group from routinely requesting a chest CT scan. They often compromise with a CXR, and only request for a

chest CT scan with intravenous contrast in the event that suspicious lesions are noted on CXR.

Patients who are to undergo long course chemoradiotherapy (LCCRT) are subjected to Cobalt radiation with a dose of Gy over a 28-day period. Doses of 5-Fluorouracil (5-FU) and Leucovorin computed at 400mg/m^2/day and 20mg/m^2/day, respectively, are administered on the first 5 days and the last 5 days of the 28-day period as continuous infusion. Patients then undergo resection of the primary tumor 6 to 10 weeks from the last day of neoadjuvant treatment.

Histopathologic reports were then reviewed. Those reporting the absence of any tumor cells were classified as having a pCR. Patients with a pathologic stage lower than the clinical or pre-treatment stage were classified as having been downstaged.

Results

There were a total of 304 rectal resections for cancer over a seven-year period. The patients' mean age was 52.7 years (range: 22 to 83). There were 168 males and 136 females (ratio 1.2:1). Fifty-three percent of patients presented with a clinical stage of Stage IIIB. (Table 1) Fifty-one percent of patients underwent either preoperative radiotherapy (14.15%) or combined chemoradiotherapy (36.82%). (Table 3) Of those who underwent long course chemoradiotherapy, 52.6 percent of tumors were downstaged. Only 21.4 percent of tumors had pCR. The highest reported pCR rate was in 2009 (30.95%). (Table 4)

The summary of the patient and tumor characteristics of the pathologic complete responders is shown in Table 5. Among patients with a pCR, the mean age was 47.22

Table 1. Distribution of rectal cancer patients undergoing resection of the primary tumor according to clinical stage, PGH, 2005-2011.

	2005		2006		2007		2008		2009		2010		2011		TOTAL	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Stage I	7	17.1	1	4	2	8.33	2	3.4	11	14.1	2	5.3	2	5.6	27	8.9
Stage IIA	9	22.0	3	12	8	33.33	15	25.9	5	6.41	10	26.3	3	8.3	53	17.4
Stage IIB	11	26.8	1	4	0	0.00	8	13.8	6	7.69	1	2.6	0	0	27	8.9
Stage IIIA	3	7.3	3	12	0	0.00	0	0.0	5	6.41	1	2.6	2	5.6	14	4.6
Stage IIIB	9	22.0	11	44	16	66.7	28	48.3	48	61.54	22	57.9	28	77.8	162	53.3
Stage IIIC	2	4.9	4	16	2	8.33	1	1.7	1	1.28	0	0	0	0	10	3.3
Stage IV	0	0	2	8	0	0	4	6.9	2	2.56	2	5.3	1	2.8	11	3.6
TOTAL	41		25		28		58		78		38		36		304	100

Table 2. Distribution of rectal cancer patients undergoing resection of the primary tumor according to pathologic stage, PGH, 2005- 2009.

	2005		2006		2007		2008		2009		2010		2011		TOTAL	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Stage 0	0	0	0	0	0	0	2	3.4	13	16.67	4	10.5	5	13.9	24	6.6
Stage I	8	19.5	5	20	7	25	13	22.4	19	24.36	2	5.3	1	2.8	55	18.1
Stage IIA	8	19.5	8	32	9	32.1	19	32.8	17	21.80	15	39.5	11	30.6	87	28.6
Stage IIB	1	2.4	4	16	5	17.9	3	5.2	6	7.69	3	7.9	0	0	22	7.2
Stage IIIA	8	19.5	2	8	0	0	2	3.4	5	6.41	0	0	1	2.8	18	5.9
Stage IIIB	7	17.1	1	4	4	14.3	6	10.3	10	12.82	8	21	8	22.2	44	14.4
Stage IIIC	3	7.3	2	8	0	0	7	12.1	6	7.69	5	13.2	8	22.2	31	10.2
Stage IV	6	14.6	3	12	3	10.7	6	10.3	2	2.56	1	2.6	2	5.6	23	7.6
TOTAL	41		25		28		58		78		38		36		304	100

Table 3. Patients with stage II-III rectal cancer undergoing neoadjuvant therapy, PGH, 2005-2011.

Year / Neoadjuvant Therapy	2005 (n=34)	2006 (n=22)	2007 (n=28)	2008 (n=52)	2009 (n=65)	2010 (n=34)	2011 (n=33)	TOTAL (n=268)
SCRT	10 (24.41%)	2 (9.09%)	5 (17.86%)	12 (23.07%)	6 (9.23%)	4 (11.76%)	4 (12.12%)	43 (16.04%)
LCCRT	5 (14.70%)	2 (9.09%)	7 (25.00%)	7 (13.46%)	42 (64.62%)	25 (73.53%)	24 (72.73%)	112 (41.79%)
TOTAL	15 (44.11%)	4 (18.18%)	12 (43.86%)	19 (36.53%)	48 (73.85%)	39 (85.29%)	28 (84.85%)	155 (57.83%)

Table 4. Frequency of tumor downstage and pathologic complete response after long course chemoradiotherapy, PGH, 2005-2011.

Year	2005 (n=5)		2006 (n=2)		2007 (n=7)		2008 (n=7)		2009 (n=30)		2010 (n=30)		2011 (n=30)		TOTAL	
Outcome	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Downstaged	4	80%	1	50%	3	42.9%	4	57.1%	33	78.6%	10	40	13	54.1	68	60.7%
Pathologic complete response	0	0%	0	0%	0	0%	2	28.6%	13	31.0%	4	16	5	20.8	24	21.4%

Table 5. Patient and tumor characteristics of patients having a pathologic complete response after long course chemoradiotherapy, PGH, 2005-2011.

Age (mean)	47.22	
Age (range)	23–72	
Gender	Male 8 (33.3%)	Female 16 (66.7%)
Histologic type	Adenocarcinoma	23 (95.8%)
	Mucinous adenocarcinoma	1 (4.2%)
Tumor grade	Well-differentiated	15 (62.5%)
	Moderately-differentiated	8 (33.3%)
	Poorly-differentiated	1 (4.2%)
Distance of tumor from anal verge (mean)	5.7cm	
Distance of tumor from anal verge (range)	3–10cm	
Preoperative	Stage I	2 (8.3%)
	Stage IIA	4 (16.7%)
	Stage IIB	2 (8.3%)
	Stage IIIB	16 (66.7%)
Surgical procedure	APR	1 (4.2%)
	Sphincter saving surgery	23 (95.8%)
Type of sphincter saving surgery	LAR	14 (60.9%)
	ATAR	9 (39.1%)

years (range 23-72 years) with 1:3 male to female ratio. The average distance FAV was 5.7 cm (range 3-10 cm). Majority presented with clinical stage IIIB (66.7%), and nearly all (95.8%) underwent a sphincter-saving operation.

Discussion

Colorectal cancer ranks fourth overall (7%) among malignancies in terms of incidence in the Philippines, as reported in the 2010 Philippine Cancer Facts and Estimates. It is the third most common malignancy (8%) affecting men and fourth most common malignancy (6%) affecting women.[11] Although colorectal cancer incidence in the United States has been declining at an average of 1.6 percent per year since 1985, the trend in the Philippines and the most of Asia appears to be increasing.[12]

Of all the colorectal cases, rectal carcinoma accounts for nearly a third of such cases and often represents a challenging entity to treat.[10] The latest report from the Philippine Cancer Society projected 5,787 new cases and 3,060 deaths from colorectal cancer in 2010.[11]

The challenge presented by rectal tumors is brought about by a combination of anatomic and biologic factors contributing to its complexity. The integration of expertise from additional disciplines such as pathology, medical and radiation oncology, and gastroenterology has allowed better understanding of the disease. This multidisciplinary approach to the treatment of rectal cancer allows for optimization of management and outcomes of patients.[9,13]

Surgery remains the most effective treatment with curative intent. Radiotherapy is being used for both resectable and non-resectable cases. As postoperative treatment, the primary aim is to decrease high local failure rates by sterilizing tumor cells left during surgery. Preoperative radiotherapy is used to "clear" peripherally located disease and induce tumor shrinkage to allow subsequent surgery to be performed with resultant adequate margins.[14]

Several randomized trials of low to moderate doses of preoperative radiation therapy (5-35 Gy) without chemotherapy have been reported. Overall, most of the trials showed a decrease in local recurrence and a subset analysis of some of the trials revealed a significant improvement in survival. The Swedish Rectal Cancer Trial, employing short-course preoperative radiation therapy (5 fractions each of 5 Gy), reported a 58 percent reduction in the rate of local recurrence[2] and an improvement in survival compared with surgery alone, with a 58 percent 5-year survival rate in the irradiated group compared with 48 percent in the non-irradiated group.[8,15-16]

Retrospective data suggest that preoperative combined modality therapy increases pathologic downstaging compared to preoperative radiation alone.[8] The European Organization for Research and Treatment of Cancer (EORTC) 22921 trial showed that the addition of chemotherapy to preoperative radiotherapy induced a significant increase of the downstaging rate. However, the long-term results (with a median follow-up of 5.4 years), failed to demonstrate a significant impact of chemotherapy, both preoperative and postoperative, on progression-free and overall survival rates.[17-18]

Other studies show that the synchronous addition of cytotoxic chemotherapy in the form of 5-fluorouracil (5-FU) to preoperative radiation increases the pCR rate over radiotherapy alone.[18] Neoadjuvant chemoradiotherapy regimens are associated with a pCR rate of approximately 4 to 33 percent.[8-9]

Data showed a downstaging rate of 52.6 percent and a pCR rate of 21.4 percent at PGH. These are comparable with international data. A rise in both dowstaging rate (78.57%) and pCR rate (30.95%) has been documented in 2009. Expectedly, more substantial results were seen with regard to tumor response to neoadjuvant treatment in 2009 because of the six-fold increase in the number of patients receiving preoperative chemoradiation from the previous years. However, we observed that only 57.33 percent of patients with an indication to receive neoadjuvant therapy went on to receive the recommended management. This was largely due to financial consideration and institutional limitation. Costs for chemoradiation have hindered patients from receiving neoadjuvant treatment. Limited facilities for radiotherapy also appear to affect decisions to forego neoadjuvant therapy. Rather than delaying cancer treatment, outright resertion of the primary tumor is

performed particularly if an adequate circumferential margin (CRM) may be achieved as assessed by CT scan.

The German Rectal Cancer Trial demonstrated the superiority of preoperative chemoradiation over postoperative chemoradiation.[17] The preoperative approach was associated with significantly lower local recurrence rates, less acute and chronic toxicity, and an increased incidence of sphincter preservation.[19] The trial from the Fédération Francophone de Cancérologie Digestive likewise showed the benefits of preoperative chemoradiation over preoperative long course radiotherapy.[26] These studies led to the formulation of the current standard of treatment for clinically diagnosed T3 (cT3) and/or node-positive disease, which is, preoperative chemoradiotherapy followed by surgery.[19]

A 5-FU-based therapy is the established chemotherapeutic regimen. It is the only combination with a mature efficacy outcome that has been compared to a standard adjuvant regimen. Variations on the infusional regimen on weeks 1 and 5 of radiation include protracted continuous-infusion 5-FU or 5-FU/Leucovorin bolus and have been extrapolated from prior large adequately powered Phase III adjuvant trials.[20] The alternative use of Capecitabine plus radiation therapy has not yet been proven to be of equal efficacy in large randomized clinical trials. However, two retrospective studies comparing 5-FU- to Capecitabine-based RT suggest equal efficacy based on pathologic downstaging and pCR data. The latest recommendation of the National Comprehensive Cancer Network (NCCN) considers Capecitabine/RT as an acceptable neoadjuvant treatment of rectal cancer.[20,21]

Randomized controlled trials in the late 1980s in the United States demonstrated improved survival among stage II and III rectal cancer patients who received neoadjuvant chemoradiation. This eventually led to a 1990 National Institutes of Health (NIH) consensus statement recommending neoadjuvant chemoradiation for patients with lymph-node positive or transmural rectal cancer.[22]

In stage I disease, local excision with or without chemoradiation is a treatment option.[10] This is considered a safe operation that should be diagnostic in most cases and potentially therapeutic in well-differentiated, superficial lesions limited to the submucosa.[23] Chemoradiation is considered in stage I disease if unexpected lymphovascular invasion is found or if there are other poor prognostic factors.[10]

In patients with locally advanced (T3–4 and/or N-positive) rectal cancer, combined modality neoadjuvant therapy improves local control and survival. Although the timing, dosage, agent, drug combination and method of delivery are controversial, patients receiving preoperative chemoradiotherapy experience reduction of tumor bulk, enhanced sphincter preservation, improved functional results, and a lower rate of acute toxicity compared with patients receiving postoperative chemoradiotherapy.[10,24] Surgical therapy consists of anterior resection (AR) or abdominoperineal resection (APR).[10,21] The use of AR as an alternative to APR allows surgeons to offer sphincter preservation without compromising survival or local recurrence. Further, the advent of the circular end-to-end anastomosis (CEEA) stapling devices has subsequently made AR with even lower pelvic anastomosis technically more feasible, and its use has become routine [9]. All resections are expectedly performed following the principles of total mesorectal excision (TME).[25]

The decision-making in Stage IV disease, on the other hand, is quite complex. Effective systemic chemotherapy has allowed improved palliative outcomes, or even cure for resectable metastases. Ultimately, decisions on management should be individualized and discussed in a multidisciplinary conference with the patient being provided a significant role in the decision-making process.

The pathologic responses of rectal cancer to the treatment modality employed are as varied as the options. In the study by Ruo and co-worker to determine whether selected clinicopathologic factors, including the extent of pathologic response to preoperative chemoradiation have an impact on long-term recurrence-free survival (RFS) in patients with locally advanced primary rectal cancer after optimal multimodality therapy, with a median follow-up of up to 69 months, the 5-year RFS for patients with pCR was 79 percent.

Another report by Glynne-Jones, et al. indicated that in proportion of patients who received preoperative chemoradiation for locally-advanced rectal cancer, only 15 to 30 percent achieved a pCR. Patients enrolled in the

German Intergroup Trial who received preoperative chemoradiation had a significant shift toward lower TNM status on pathologic staging, including a pCR in 8 percent of patients.[26,27]

An initial observational study in Brazil that proposed the concept of closely observing patients with clinical complete response after chemoradiation for locally advanced rectal cancer has been enthusiastically received.[18] In a study by Habr-gama, 71 patients were observed rather than proceeding to surgery after neoadjuvant therapy. This approach is contrary to institutional practices and is extrapolated from the successful achievements in the treatment of squamous cell carcinoma of the anus, for which it is generally agreed upon that primary chemoradiation, and not surgery, is the initial treatment of choice.[18]

Adopting a "wait and see" strategy might be appropriate for selected low cT1 or cT2 tumors in which local excision is not initially feasible, or the patient is unfit or unwilling to undergo radical surgery, which may require the formation of a permanent stoma. However, the validity of this approach relies on poorly reported and inadequately documented retrospective observations. The available evidence remains insufficient to support this policy, and may not be robust enough to risk the well-being of a young, fit patient, although it could be justified for early-stage tumors in elderly patients with considerable co-morbidity.[18]

An aspect of preoperative chemoradiation that has been fully evaluated in literature is the subset of patients who experience tumor progression during the course of treatment. The authors are in the process of analyzing available data on these patients. In their review, two patients with tumor progression were encountered. These patients, not having met the inclusion criteria (the first patient did not undergo resection of the primary, while the second patient had metastatic disease) were excluded from the computations for this study.

The UP-PGH Colorectal Cancer and Polyp Study Group, formed in 2007, has been at the fore of rectal cancer management since its establishment. The increased utilization of neoadjuvant chemoradiation for rectal cancer and the expected rise in dowstaging and pCR rates may be explained by a broader understanding of principles of management of rectal cancer and improved communication among the different specialties. Despite the presence of various limitations, the Group's downstaging and pCR rates are comparable with international data. They presented the first available local data accumulated to report on this breakthrough in rectal cancer treatment.

Conclusion

The utilization of neoadjuvant chemoradiation as presented has shown comparable outcomes to those reported in foreign literature on rates of downstaging and pCR. A more protracted study should be pursued to assess for long-term outcomes regarding recurrence and survival.

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