

Comparative Study Between Whole Brain Radiotherapy And Concurrent Temozolomide Versus Whole Brain Radiotherapy Alone For Patients Of Brain Metastasis

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Abstract

Background- The study aimed to assess the safety and efficacy of temozolomide along with whole brain radiotherapy in brain metastasis and compare with the efficacy and safety of WBRT alone.

Methodology- This study was conducted as a prospective study at Department of Radiotherapy, NSCB Medical College Jabalpur during the study period of 20 months among 34 radiologically and histologically proven case of brain metastasis patients. All the patients were randomly divided into two groups cases (WBRT with TMZ) and controls (WBRT). Two groups were compared for radiological response, symptoms and adverse reactions weekly upto 6 weeks.

Results- In week 2, hematological derangement were observed in significantly higher proportions of cases as compared to control ($p<0.05$). Vomiting and seizure was noted in significantly higher proportions of controls at week 4 following treatment ($p<0.05$). Though the radiological response was better in cases but the observed difference between cases and controls was statistically insignificant ($p>0.05$).

Conclusions- Brain metastasis following primary cancer are commonly observed in cancer clinics. WBRT is given for palliative treatment in such patients. However, addition of TMZ had shown symptomatic improvement in patients with brain metastasis. Though, adverse events especially hematological were reported in higher proportions with TMZ, but these adverse effects could be effectively managed. Overall, TMZ is associated with good response rate. Thus, it can be added to WBRT to improve the survival rate and response rate in patients with brain metastasis.

Introduction

According to the World Health Organisation (WHO), metastatic tumours of the central nervous system (CNS) are defined as “tumours that primarily originate outside the CNS and spread secondarily to the CNS via the hematogenous route (metastasis) or by direct invasion from adjacent tissues”.^[1] Brain metastasis secondary to systemic cancers are estimated to be 10 times more common as compared to primary malignancy of brain.^[2] Metastasis to brain following primary tumor has been estimated to be as high as 40% and the probability of brain metastasis depend upon the pathological characteristics of primary tumour.^[2] Brain metastasis is commonly results secondary to primary malignancy of lung, breast, melanoma, prostate and head and neck cancers.^[3,4]

Metastatic cancer from primary tumor enters the CNS via blood stream. The cells then proliferate at the site of metastasis leading to local invasion, inflammation, edema as well as displacement. Brain metastasis is most common among various forms of intracranial metastasis, which is attributed to high blood flow.^[4] Neuroimaging modalities such as CT scan and MRI plays an important role in diagnosis of metastasis, determining the extent of lesion, staging of cancer as well as in deciding management modality among these patients.^[5,6]

The brain metastasis is usually associated with poor prognosis and decision regarding treatment modality is one of the critical step among these patients as the prognosis even after surgery remains poor and is indicated for palliative care. Presently, surgery and stereotactic radiotherapy are considered as an optimal protocols for the palliative therapy which are advisable especially in case of single nidus. However, for the management of brain metastasis with multiple nidi, whole brain radiotherapy (WBRT) is most commonly indicated.^[7] Literature suggest that whole brain radiotherapy when implemented accurately may help in providing symptomatic relief and also prolong survival of patients with brain metastasis.^[8,9]

Concurrent Temozolomide administration with whole brain radiotherapy has shown to have additive effect in management of brain metastasis.^[10] Literature suggest that concomitant WBRT with Temozolomide followed by Temozolomide therapy in patients with primary CNS tumors such as glioblastoma multiforme to be both effective and safe.^[11,12] Despite standard treatment with whole brain radiotherapy, it is difficult to achieve complete remission in most cases, which makes survival rate and overall prognosis poor. Thus, in order to achieve better disease control and improve prognosis, many attempts have been made. The efficacy of WBRT with Temozolomide has been conducted in Western population, however, data is scarce in Indian scenario. The present study was thus conducted at tertiary care centre to assess the safety and efficacy of temozolomide along with whole brain radiotherapy in brain metastasis and compare with the efficacy and safety of WBRT alone.

Methodology

The present study was conducted as a prospective, randomized study at Department of Radiotherapy, Government Cancer Hospital, Netaji Subhash Chandra Bose Medical College Jabalpur during the study period of 20 months i.e. from 1st Jan 2019 to 31st August 2020. All 34 Patients with radiologically and histologically proven case of brain metastasis belonging to age range of 18 to 70 years with KPS of more than 40 and ECOG performance status of 0-2 were included in study. However, patients with uncontrolled comorbidity, hypersensitivity to temozolomide, previous history of cranial radiation were excluded from the study.

After obtaining approval of college ethics committee and informed consent, all the patients fulfilling the inclusion criteria were enrolled and were randomly divided into two groups.

Cases- In this group patients received WBRT 30Gy/10# with concurrent temozolomide 75mg/m² PO daily

Control- In this group patients were given only WBRT 30Gy/10#

Detailed data regarding sociodemographic details was obtained from all the study participants such as age, gender, education, income, socioeconomic status etc. and noted in pretested semi-structured questionnaire. All the patients were subjected to detailed history regarding presenting symptoms with special emphasis on neurological symptoms. Further all the patients were subjected to detailed general

physical examination. Detailed neurological examination was also conducted and findings were noted in questionnaire.

Further, lab investigations were conducted which included chest X-ray, USG abdomen pelvis for primary disease status, CBC, LFT, RFT etc. CECT/ MRI BRAIN were conducted at baseline and at 4 to 6 weeks after treatment

Radiotherapy treatment protocol given in present study (both Arms):-Patients were given External Beam Radiotherapy which was delivered by Co⁶⁰ Teletherapy machine. By doing planning x ray of skull. EBRT in a dose of 300cGy per fraction 5 # weekly for 10 days upto 3000cGy with total duration of 2 weeks was given using Parallel opposing bilateral fields at 80cm SSD.

Concurrent Chemotherapy protocol schedule (case group)- Cases were given daily temozolomide 75 mg/m² oral empty stomach till completion of radiotherapy

Patients (both control & group group) were assessed weekly for local neurological assessment & development of adverse reactions such as diarrhoea, skin haematological toxicity. Grading of diarrhoea and mucosal reactions was done as per WHO criteria. Grading of toxicity was done by CTCAE criteria Haematological & renal function test will be evaluated weekly during treatment.^[13] Patient were evaluated at the end of treatment completion and 4 to 6 weeks after treatment. Radiological response was evaluated in terms of Stable Disease (SD), Partial Response (PR), Progressive Disease (PD) or Complete Response (CR).On basis of RECIST 1.1 criteria^[14], and symptoms resolution at completion of radiotherapy

Statistical Analysis-Data was compiled using MsExcel and analysed using IBM SPSS software version 20. Data was grouped and expressed as frequency and percentage whereas numerical data was expressed as mean and SD. Chi square test was applied to assess the difference in proportions of two groups whereas unpaired t test was applied to assess the difference in mean between two groups. P value less than 0.05 was considered statistically significant.

Results

The study was conducted on total of 34 patients who presented with brain metastasis following primary cancer. Patients were divided into two groups i.e. cases and control comprising of 17 patients each.

Mean age of cases was 51.53±11.50 years whereas mean age of controls was 45.47±11.93 years. Majority of patients in case group belonged to 41 to 50 years of age (35.3%) whereas majority of controls belonged to less than 40 years of age. About 58.8% cases and 64.7% controls were females. Majority of patients were resident of rural area and majority of patients belonged to lower socioeconomic status. Two groups were comparable with respect to sociodemographic variables ($p>0.05$).

The present study documented no statistically significant difference in tumour characteristic of patients of two groups ($p>0.05$). Mean GPA in cases was 1.35 ± 1.08 whereas mean GPA among controls was 1.82 ± 0.89 . About 23.5% cases had GPA 0 whereas majority i.e. 76.5% controls had GPA of 2. The observed difference in GPA between cases and controls was statistically highly significant ($p<0.01$).

In week 2, hematological derangement were observed in significantly higher proportions of cases as compared to control ($p<0.05$) whereas no such difference was observed between cases and controls for other adverse effects.

Our study documented no statistically significant difference in headache between cases and controls at presentation, during first, second and fourth week following treatment ($p>0.05$). In present study, vomiting and seizure was noted in significantly higher proportions of controls at presentation and at week 4 following treatment ($p<0.05$). Other symptoms were observed in significantly higher proportions of cases (35.3%) as compared to controls (5.9%) during all the follow up ($p<0.05$).

Complete response was observed in 5.9% cases. However, partial response was observed in equal proportions of cases as well as control (70.6%). Stable disease was observed in 23.5% cases whereas disease was progressive in 23.5% controls. Though the response was better in cases but the observed difference between cases and controls was statistically insignificant ($p>0.05$).

Discussions

Brain metastasis are one of the most common type of intracranial metastases and are 10 times more common as compared to primary malignancy of brain.^[2] Brain metastasis commonly develop from primary tumors of lung, breast, and melanoma.^[3,4] Presence of metastasis to brain is poor prognostic feature and whole brain radiotherapy (WBRT) is most commonly indicated for management of such patients.^[7] Temozolomide (TMZ), an orally administered chemotherapeutic agent that cross the blood-brain barrier has shown to have additive effect in management of brain metastasis.^[11] The present study aimed at assessing and comparing radiological, clinical response and side effects before and after treatment in two groups i.e. cases (WBRT with TMZ) and controls (WBRT alone).

Brain metastasis is commonly observed following primary cancers affecting lung, breast, and melanoma. Other malignancies less commonly associated with brain metastasis included prostate and head and neck cancers.^[3,4] Primary cancer histology is an important determinant of aggressiveness of cancer. In present study, majority of cases (47.1) as well as controls (52.9%) presented with brain metastasis following carcinoma breast followed by Ca lung (29.4% cases and 23.5% controls). Other primary sites were Ca oropharynx, Ca rectum, ca urinary bladder, Melanoma, Ca cervix and Ca gastroesophageal junction. In present study, as majority of patients had breast cancer, the histology in majority of cases (41.2%) and controls (52.9%) was intraductal carcinoma whereas about 23.5% and 35.3% cases and controls respectively were adenocarcinoma. However, two groups comparable with respect to primary histology ($p>0.05$). Previous literature mainly included brain metastasis following primary lung cancer or

primary breast cancer or ovarian cancers individually. In another meta-analysis by Xin et al^[15] and Lv et al^[16] included patients with brain metastases (BM) from non-small-cell lung cancer (NSCLC). However in a study by Zhao et al, majority of patients presented with brain metastasis following lung cancer followed by breast cancer.^[17]

Karnofsky performance status (KPS) and graded prognostic assessment (GPA) are important indicators helpful in assessing the prognosis of patients with brain metastasis. The Radiation Therapy Oncology Group (RTOG) recently recommended disease specific graded prognostic assessment (GPA) for patients with brain metastasis.^[18] The GPA has been divided into 4 groups i.e. 0-1 (median survival- 2.6 months), GPA 1.5-2.5 (3.8 months); GPA 3 (6.9 months) and GPA 3.5-4.0 (11 months). In present study, majority of cases i.e. 47.1% and controls (52.9%) belonged to KPS grade of 80 and about 23.5% cases had GPA 0 whereas majority (76.5%) of controls had GPA of 2. Thus, WBRT with TMZ was given to significantly higher proportions of patients with lower GPA whereas WBRT alone was given in significantly higher proportions of controls ($p<0.01$). However, the two groups were comparable with respect to KPS ($p>0.05$).

Toxicity following management is particularly relevant in the treatment of brain metastases, as they further deteriorate the morbidity and quality of life of patient. In present study, though nausea was observed in almost equal proportions of cases and controls during week 1 and week 2, but severity of nausea higher in controls but the difference was statistically insignificant ($p>0.05$). Similarly, no significant difference was observed between cases and controls for vomiting, diarrhea ($p>0.05$). Hematological effect were adverse in significantly higher proportions of cases as compared to controls at week 2 ($p<0.05$). Hepatic, renal involvement and radiation dermatitis was neither observed in cases nor in controls. The findings of present study were concordant with the findings of Liu et al in which hematological and gastrointestinal adverse effects were observed in higher proportions of cases and controls but the difference was statistically significant ($P > 0.05$).^[19] Zhao et al in however observed contrasting findings as compared to present study. They documented that RT plus TMZ arm was associated with significantly more grade 3 to 4 nausea and thrombocytopenia.^[17] Yong et al^[20] and Deng et al^[21] concluded that though TMZ in combination with WBRT is associated with higher incidence of adverse events particularly nausea and thrombocytopenia but patients can tolerate these effects and can be managed using medications.

The present study documented no statistically significant difference symptomatic response between cases and controls for headache and blurring of vision ($p>0.05$). However, vomiting was observed in significantly higher proportions in cases as compared to controls ($p<0.05$) whereas seizures were documented in significantly higher proportions of controls ($p<0.05$) during fourth week follow up. These findings were concordant with the findings of Liu et al in which the authors observed symptomatic improvement during and 4–6 weeks after treatment in significantly higher proportions of patients in observation group (94.4%) as compared to control groups (63.89%) ($P = 0.0014$).^[20] As TMZ is itself associated with nausea and vomiting, and hence the symptomatic response for GI symptoms was significantly lower among cases as compared to controls ($p<0.05$) in our study.

Though, overall response was better in cases as compared to controls, but the difference was statistically insignificant ($p>0.05$) in present study. Complete response was observed in one patient in case group whereas partial response was observed in 70.6% cases and controls each. Stable disease was observed in 23.5% cases whereas disease was progressive in 23.5% controls. These findings were concordant with the findings of Zhu et al in which the authors observed significantly better improvement in TMZ + WBRT arm as compared to WBRT alone in ORR ($P = 0.0108$).^[22] Similarly, Xin et al observed statistically significant better overall response rate in WBRT with TMZ group as compared to WBRT alone group ($p<0.05$).^[15]

Conclusions

Brain metastasis following primary cancer are commonly observed in cancer clinics. The prognosis is worse even after treatment. Whole brain radiotherapy is given for palliative treatment in such patients. However, addition of TMZ, a chemotherapeutic agent have shown symptomatic improvement in patients with brain metastasis. Though, adverse events especially hematological were reported in higher proportions of patients receiving TMZ, but this does not led the patient to discontinue the treatment. These adverse effects could be effectively managed. Overall, TMZ is associated with good response rate. Thus, it can be added to WBRT to improve the survival rate and response rate in patients with brain metastasis.

I here by declare that there is no conflict on interest.

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Tables

Table 1
Distribution of patients according to sociodemographic variables

Sociodemographic variables	Group		P value
	Case (n = 17)	Control (n = 17)	
Age	≤ 40	3 (17.6)	7 (41.2)
	41–50	6 (35.3)	5 (29.4)
	51–60	3 (17.6)	4 (23.5)
	> 60	5 (29.4)	1 (5.9)
Gender	Male	7 (41.2)	6 (35.3)
	Female	10 (58.8)	11 (64.7)
Residence	Rural	11 (64.7)	11 (64.7)
	Urban	6 (35.3)	6 (35.3)
SES	Lower	12 (70.6)	14 (82.4)
	Middle	3 (17.6)	3 (17.6)
	Upper	2 (11.8)	0 (0.0)

Table 2
Distribution of patients according to tumour characteristics

Characteristics	Group		P value
	Case (n = 17)	Control (n = 17)	
PRIMARY DIAGNOSIS			
Ca Breast	8(47.1)	9(52.9)	0.52
Ca Cervix	1(5.9)	0(0.0)	
Ca GEJ	0(0.0)	1(5.9)	
Ca Lung	5(29.4)	4(23.5)	
Ca Oropharynx	2(11.8)	0(0.0)	
Ca Rectum	1(5.9)	1(5.9)	
Ca Bladder	0(0.0)	1(5.9)	
Melanoma	0(0.0)	1(5.9)	
Histology			
Adenocarcinoma	4(23.5)	6(35.3)	0.28
Adenoid + Neuroendocrine Ca	1(5.9)	0(0.0)	
IDC	7(41.2)	9(52.9)	
Invasive Carcinoma	1(5.9)	0(0.0)	
MDKCC	3(17.6)	0(0.0)	
Melanoma	0(0.0)	1(5.9)	
SCC	1(5.9)	0(0.0)	
Transitional Cell Carcinoma	0(0.0)	1(5.9)	
KPS			
60	2(11.8)	3(17.6)	0.87
70	5(29.4)	4(23.5)	
80	8(47.1)	9(52.9)	
90	2(11.8)	1(5.9)	

Table 3
Distribution of patients according to adverse event during treatment

Adverse event during treatment			Case (n = 17)	Control (n = 17)	χ^2	P value
Nausea	Week 1	Absent	2(11.8)	2(11.8)		
		1	15(88.2)	14(82.4)		
		2	0(0.0)	1(5.9)		
	Week 2	Absent	9(52.9)	6(35.3)	1.67	0.435
		1	7(41.2)	8(47.1)		
		2	1(5.9)	3(17.6)		
Vomiting	Week 1	Absent	3(17.6)	2(11.8)	0.52	0.769
		1	10(58.8)	12(70.6)		
		2	4(23.5)	3(17.6)		
	Week 2	Absent	8(47.1)	5(29.4)	1.22	0.543
		1	7(41.2)	10(58.8)		
		2	2(11.8)	2(11.8)		
Diarrhea	Week 1	Absent	17(100.0)	17(100.0)	NA	NA
	Week 2	Absent	16(94.1)	17(100.0)	1.03	0.311
		1	1(5.9)	0(0.0)		
Radiation dermatitis	Week 1	Absent	17(100.0)	17(100.0)	NA	NA
	Week 2	Absent	17(100.0)	17(100.0)	NA	NA
Hematological	Week 1	Absent	12(70.6)	17(100.0)	5.86	0.053
		1	4(23.5)	0(0.0)		
		2	1(5.9)	0(0.0)		
	Week 2	Absent	11(64.7)	17(100.0)	7.28	0.026
		1	5(29.4)	0(0.0)		
		2	1(5.9)	0(0.0)		
Renal	Week 1	Absent	17(100.0)	17(100.0)	NA	NA
	Week 2	Absent	17(100.0)	17(100.0)	NA	NA
Hepatic	Week 1	Absent	17(100.0)	17(100.0)	NA	NA

Adverse event during treatment	Case (n = 17)	Control (n = 17)	χ^2	P value
Week 2 Absent	17(100.0)	17(100.0)	NA	NA

Table 4
Distribution of patients according to symptomatic response

Symptomatic response			Case (n = 17)	Control (n = 17)	P value
Headache	Presentation	Absent	3(17.6)	3(17.6)	0.49
		3 10	3(17.6)	3(17.6)	
		4 10	4(23.5)	7(41.2)	
		5 10	7(41.2)	3(17.6)	
		6 10	0(0.0)	1(5.9)	
	Week 1	Absent	5(29.4)	3(17.7)	0.263
		2/10	2(11.8)	1(5.9)	
		3/10	4(23.5)	10(58.8)	
		4/10	5(29.4)	2(11.8)	
		5/10	1(5.9)	1(5.9)	
	Week 2	Absent	5(29.4)	3(17.7)	0.438
		1/10	3(17.6)	2(11.8)	
		2/10	5(29.4)	9(52.9)	
		3/10	4(23.5)	3(17.6)	
	Week 4	Absent	5(29.4)	3(17.7)	0.302
		1/10	11(64.7)	14(82.4)	
		2/10	1(5.9)	0(0.0)	
Vomiting	Presentation		8(47.1)	14(82.4)	0.031
			8(47.1)	6(35.3)	0.489
			9(52.9)	13(76.5)	0.151
			9(52.9)	15(88.2)	0.024
Seizure	Presentation		1 (5.9)	4 (23.5)	0.146
			1(5.9)	1(5.9)	1.00
			1(5.9)	1(5.9)	1.00
			1(5.9)	4(23.5)	0.001
Blurring of Vision	Presentation		2 (11.8)	7 (41.2)	0.052
			1(5.9)	3(17.6)	0.287

Symptomatic response		Case (n = 17)	Control (n = 17)	P value
	Week 2	1(5.9)	5(29.4)	0.072
	Week 4	1(5.9)	5(29.4)	0.072
Others	Presentation	10 (58.8)	5 (29.4)	0.084
	Week 1	6(35.3)	1(5.9)	0.034
	Week 2	6(35.3)	1(5.9)	0.034
	Week 4	6(35.3)	1(5.9)	0.034

Figures

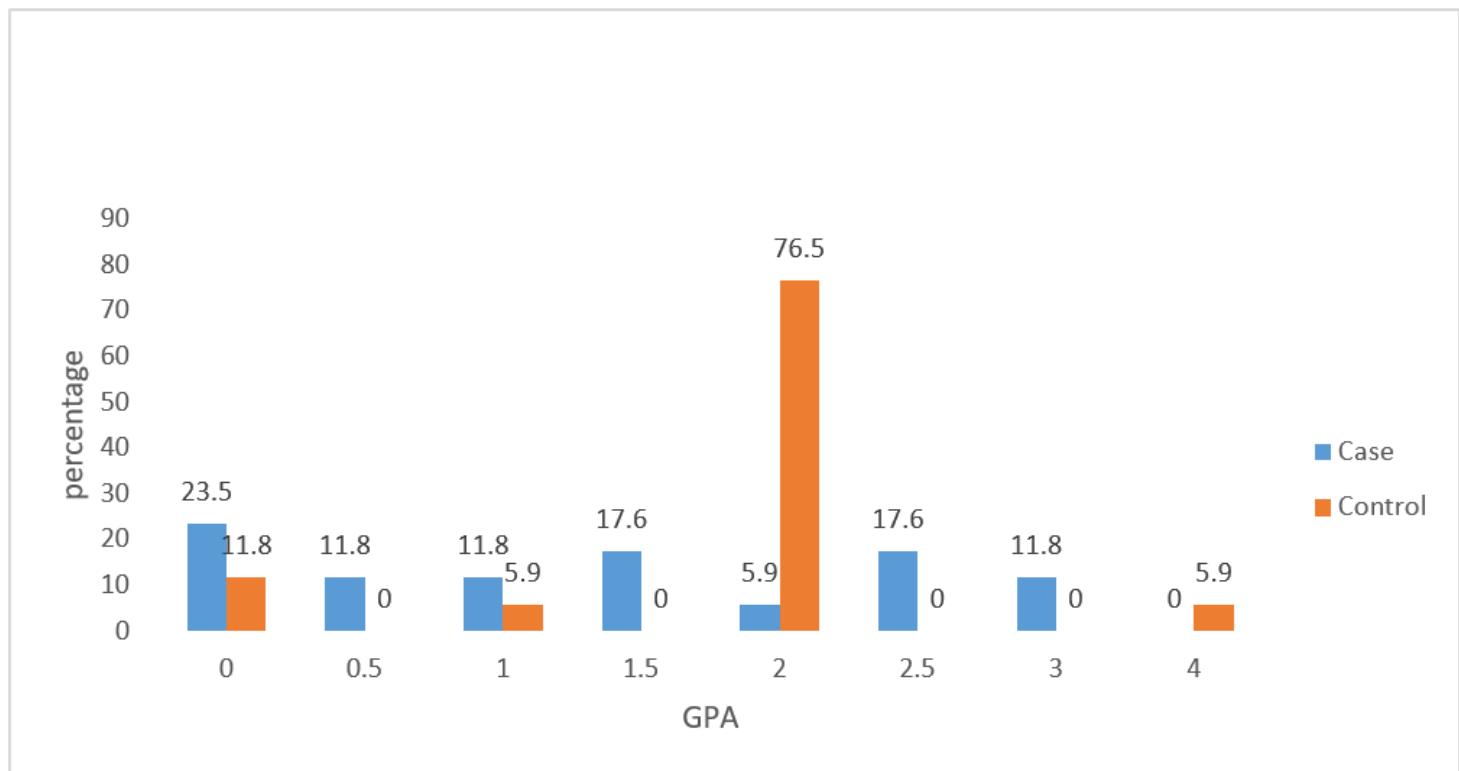


Figure 1

Distribution of patients according to GPA

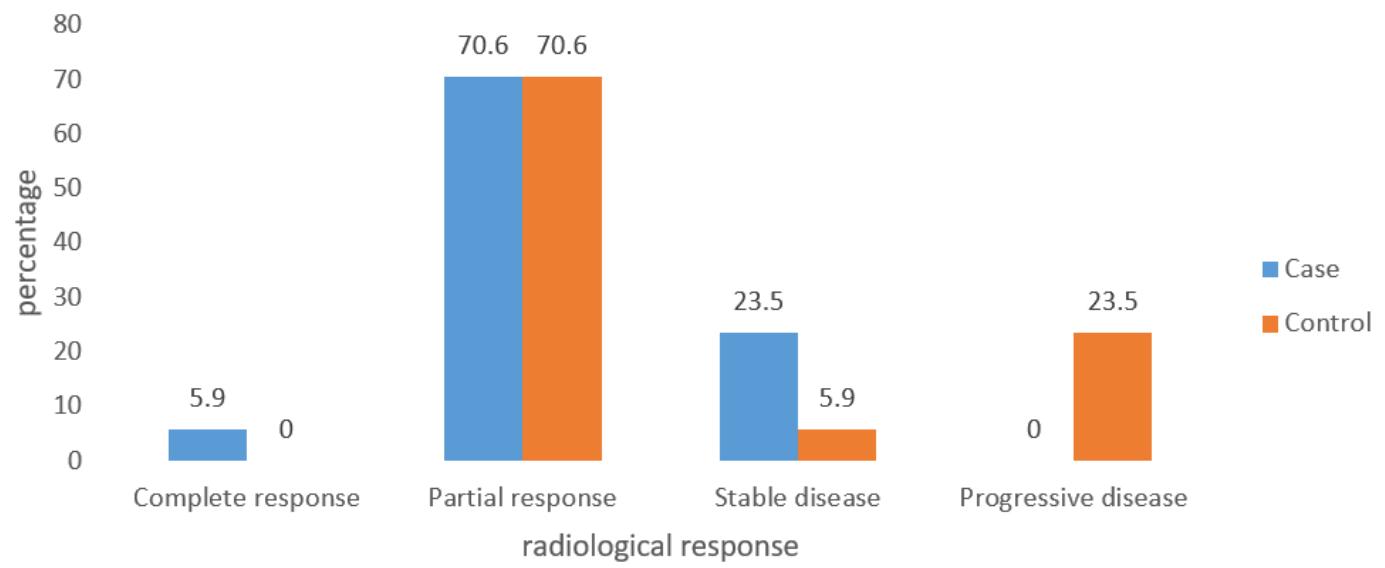


Figure 2

Distribution of patients according to radiological response