Original paper

Outcome of Pediatric Low Grade Gliomas in Developing Countries: the Impact of Elimination of Radiotherapy

Usama Ahmed Al-Jumaily^*
^Departments of Pediatric, Medical College of Kerbalaa University, Kerbalaa, Iraq

Abstract

Background: The care of pediatric low grade gliomas (LGG) of central nervous system in developing countries is still suboptimal. By introduction of chemotherapy and avoiding of radiotherapy in children, better outcome should be achievable.
Objectives: to evaluate the impact of replacement of radiotherapy by chemotherapy on the survival rate for children with LGG.
Methods: A retrospective study was conducted of records of patients (n=85; 48 males; median age 6 years) with LGG from May 2003 to December 2009 at King Hussein Cancer Center, Jordan. Patient demographics, tumor characteristics, treatment plan, and outcomes were studied.
Results: Five-year event free survival (EFS) and overall survival (OS) rates were 60%±7.3% and 92%±4.1%, respectively. The most common tumor site was the Posterior fossa/cerebellum and the suprasellar/hypothalamic area (n=23 each). The most common pathologic diagnosis was pilocytic astrocytoma (n=62). Initial surgical interventions were gross total resection (n=21), subtotal resection (n=20), and partial resection/biopsy (n=39). Posterior fossa tumors were more likely to have gross total or subtotal resection (n=17) compared to tumors in other sites. The most commonly used chemotherapeutic regimen was carboplatin/vincristine (n=29) followed by Vinblastine (n=6). There was a significant difference in the 5-year EFS by the tumor location (P=0.048) and degree of surgical resection (P=0.023). There was no statistical significance in outcome by the type of chemotherapy used (P=0.57).
Conclusions: LGG management in developing countries can be improved through a multidisciplinary approach. The main impact of this approach was the elimination of radiotherapy from the management of most patients with LGG.
keywords: Low grade gliomas, chemotherapy, developing countries

Introduction

Low grade gliomas (LGG) represent approximately one third of all childhood brain tumors. Although they are assumed to have a benign course, less is known about the outcome of such tumors. Complete surgical resection is the cornerstone of the treatment, resulting in cure in the vast majority of children [1-3].
When complete gross resection is invalid, other options like radiotherapy and chemotherapy are to be considered. Radiotherapy approach is less appealing because of the well-known harmful side effects especially in younger age group [4]. Nowadays chemotherapy has been used to delay radiotherapy and its major negative impact on the growing nervous system; it is widely acceptable in LGG especially in optic pathways and opticochiasmatic tumors due to limitations of complete surgery. It appears clear that some drugs like vincristine, carboplatin, vinblastine, nitrosureas, cisplatin, and etoposide are effective and can induce objective tumor response in a good percentage of patients; the response rate has been reported to range from 52-62% [5-8].
Despite improved outcomes of children with LGG in developed countries, management of
LGG in developing countries is suboptimal. Obstacles to the management

*For Correspondence: E-Mail drusama2004@yahoo.com

of LGG in developing nations include complexity of treatment, lack of concept of multidisciplinary approach, and use of radiotherapy as a principal modality of treatment without awareness of its long term sequel.

To evaluate how a multimodal approach, telemedicine and twinning initiative worked well for a center in a developing nation, we conducted in this study a 5-year retrospective chart review of the clinical characteristics, multiagent treatment plan, and outcomes of children with LGG treated at a single center.

Materials and Methods

Patients

A retrospective review of the medical records of children with LGG (May 2003 to December 2009) at King Hussein Cancer Center, Amman, Jordan, who were younger than 18 years at the time of diagnosis was conducted at KHCC. Data were retrieved from medical records and pathology databases.

Patients with tumors interpreted as low-grade (i.e., WHO grades I and II), as described by the revised WHO classification in 1993 [9], were included in this study.

We reviewed patients' characteristics [demographics, tumor location, presence of neurofibromatosis (NF-1) features, extent of tumor resection, cerebro-spinal fluid (CSF) shunting, pathology], treatment plan (chemotherapy agents, initial, second- or third-look surgery, and radiotherapy), and outcomes [5-year event-free survival (EFS) and OS].

Most of the patients were discussed in the neuro-oncology multidisciplinary clinic (MDC) including of pediatric oncologists, pediatric neurosurgeons, radiation oncologists, radiologists, pathologists, and psycho-social team, once weekly and the treatment plan was decided; complicated or difficult cases were discussed with experts at hospital for sick children (HSC) in Canada/Toronto through monthly teleconferences; by each telemedicine 4-5 cases with CNS tumors were discussed including children with LGG over 1 hour; cases who needed urgent consultation were sent by emails.

Surgery

Surgical resection was categorized as gross total resection (GTR), complete removal with no residual tumor by the operative report; subtotal resection (STR), 50-99% reduction in tumor by surgeon`s report; and partial resection (PR)/biopsy, less than 50% reduction in tumor. Postoperative computed tomography (CT) or magnetic resonance imaging (MRI) was used to confirm extent of resection.

The goal of surgery was to achieve a wide and complete resection of the primary tumor wherever feasible without causing major neurological sequel. In some sites where complete surgical resection is not doable (e.g., pituitary/hypothalamic tumors), biopsy or subtotal resection (STR) was performed. Surgical resection was performed at the initial and/or subsequent operations wherever possible and reasonable or when there is tumor progression during the course of treatment.

In some cases, specifically optic nerve pathway gliomas, the diagnosis of LGG was made by a radiological appearance, as surgery (i.e., open biopsy) offered no noteworthy benefit for the diagnosis as well as its association with major surgical complications [10].

Chemotherapy protocol

The chemotherapy regimen was similar to that used in developed countries. The first chemotherapy regimen is carboplatin/vincristine [11], with a dose of 560mg/m2 for the carboplatin, and 1.5mg/m2 for the vincristine, every three weeks for 1 year; the 2nd line of treatment is Vinblastine weekly, with a dose of 6mg/m2/week, for 1 or 2 years [8, 12], which is used in case of tumor progression with the 1st regimen, life threating complications due to chemotherapeutic drugs (e.g., anaphylactic reactions due to

carboplatin), or at the discretion of the parents. Cisplatin/Etoposide regimen (a 10 monthly cycles of cisplatin, 30 mg/m2/d on days 1 to 3, and etoposide, 150 mg/m2/d on days 1 to 3) [13], or thioguanine, procarbazine, CCNU, vincristine (TPCV) regimen (an 8 cycles with 6 weeks intervals of thioguanine, 30 mg/m² P.O. q 6 hours for 12 doses Days 0-2, procarbazine, 50 mg/m² q 6 hours P.O. for 4 doses Days 2-3, CCNU, 110 mg/m² P.O. Day 3, and vincristine, 1.5 mg/m² on days 14 and 28) [14] can be used as a third or fourth chemotherapy treatment option in case of treatment failure to the 1st and 2nd chemotherapy regimen.

Radiotherapy

Radiotherapy was omitted unless there is no response to all chemotherapeutic regimens. One of the major rule of the treatment is to postpone radiotherapy as much as possible to protect the child`s brain and avoid late sequel and adverse effects of radiotherapy on the growing brain. The dose of radiotherapy was delivered according to the tolerance dose of the neighboring structures, avoiding major adverse effects.

Radiology

All through the study period, patients were routinely imaged using a high quality MRI (AVANTO 1.5 and INGENIA 3/TESLA) and/or CT scan (VOLUME ZOOM 8 and BRILLIANCE 64/PHILLIPS). Radiologic images were interpreted by a pediatric radiologist who routinely attended the multidisciplinary clinic (MDC) and telemedicine.

Pathology

All samples were reviewed in the center by a board certified pathologist. Difficult cases were discussed in the telemedicine and some samples may be sent to experts in developed countries for second opinion.

Statistical analyses

Event-free survival (EFS) was defined as the time from the date of diagnosis to disease recurrence or death as a first event. Overall survival (OS) was defined as the time from date of diagnosis to death from any cause or lost to follow-up. The Kaplan-Meier method was used to estimate EFS and OS distributions. Differences between survival curves between the 1st and 2nd chemotherapy regimens were analyzed by the log-rank test. The statistical level with a P value of less than or equal to 0.05 was considered significant.

Results

Patients' characteristics

Demographics

From May 2003 to December 2009, 85 patients less than 18 year old with LGG were enrolled in this study at King Hussein Cancer Center (KHCC), Amman, Jordan. There were 48 males (56%) and 37 females (44%) with a median age of 6 years (range 0.5–17 years). The median follow up was 38.5 months and the range was between 1-115 months (table 1).

Tumor sites

Of the 85 patients, 23 (27%) had a tumor at the posterior fossa/cerebellum site and another 23 (27%) had a tumor at the suprasellar/hypothalamic area; the next most common site of involvement was at the cerebrum (seventeen patients; i.e.; 20%) ; only 6 (7%) patients had a tumor at the spinal cord; 4 (4.7%) patients had tumors at the cervicomedullary, pineal, and thalamic sites for each; only one patient had a tumor at the brain stem (pons) area (table 1).

Pathological diagnosis

Of the 85 patients, 62 (73%) had pilocytic astrocytoma histology, 6 (7%) had pilomyxoid astrocytoma histology, 5 (5.9%) had ganglioglioma, 3 (3.5%) had DNET (Dysembryoplastic Neuro Epithelial tumor) histology, 2 (2.3%) had DIG (Desmoplastic Infantile Ganglioglioma), 1 (1.1%) patient had a fibrillary astrocytoma histology and another 1 (1.1%) had SEGA (Sub Ependymal Giant cell tumor); in 5 (5.9%) cases there was no histological biopsy and

the diagnosis was established depending on the radiological appearance (table 1).

Table 1. patient characteristics

Gender		Age (years)	
Male	48 (56%)	Median	6
Female	37 (44%)	Range	0.5 - 17
Tumor site		Pathology Diagnosis	
Brain stem	1 (1.1%)	Pilocytic astrocytoma	62 (73%)
Cerebrum	17 (20%)	Pilomyxoid astrocytoma	6 (7%)
Cervicomedullary	4 (4.7%)	Fibrillary astrocytoma	1 (1.1%)
Optic nerve	4 (4.7%)	Ganglioglioma	5 (5.9%)
Pineal	3 (3.5%)	DIG	2 (2.3%)
Posterior fossa/cerebellum	23 (27%)	DNET	3 (3.5%)
Spinal	6 (7%)	SEGA	1 (1.1%)
Suprasellar/hypothalamic	23 (27%)	No biopsy was done	5 (5.9%)
Thalamus	4 (4.7%)		

DIG, Desmoplastic Infantile Ganglioglioma; DNET, Dysembryoplastic Neuro Epithelial tumor; SEGA, Sub Ependymal Giant cell tumor

Surgery

For those patients who underwent the 1st surgical approach (n= 80), 21 (25%) had GTR, 20 (24%) had STR, and 39 (45%) had PR/biopsy; 5 (6%) patients did not undergo any surgical intervention.

For those patients who underwent the 2nd surgery (n= 21), 1 had GTR, 10 had STR, and another 10 had PR; for those who have had the third surgery (n=4), 2 had STR and another 2 had PR (table 2).

Table 2. Extension of surgery

First surgery	
GTR	21 (25%)
STR	20 (24%)
Biopsy/PR	39 (45%)
No surgical intervention	5 (6%)
Second Surgery (n= 21)	
GTR	1 (4.7%)
STR	10 (47.6%)
PR	10 (47.6%)
Third Surgery (n= 4)	
STR	2
PR	2

GTR, gross total resection; STR, subtotal resection; PR, partial resection

Chemotherapy

Thirty nine patients were given the 1st line of chemotherapy regimen; 29 of them received the carboplatin/vincristine regimen, 6 patients received vinblastine regimen, and another 4 patients received other types of chemotherapy; from those who received the carboplatin/vincristine regimen, 14 developed anaphylactic reactions, 9 of them were given the vinblastine regimen and the other 5 were kept for observation.

Thirteen patients received the 2nd line of chemotherapy, 2 were given the carboplatin/vincristine regimen, and 11 were given the vinblastine regimen (9 of them developed anaphylaxis to carboplatin/vincristine regimen).

Only 6 patients underwent to the 3rd line of chemotherapy, 5 received TPCV chemotherapy regimen (thioguanin/ procarbazine/ CCNU/vincristine) regimen, and only one was given vinblastine (figure 1).

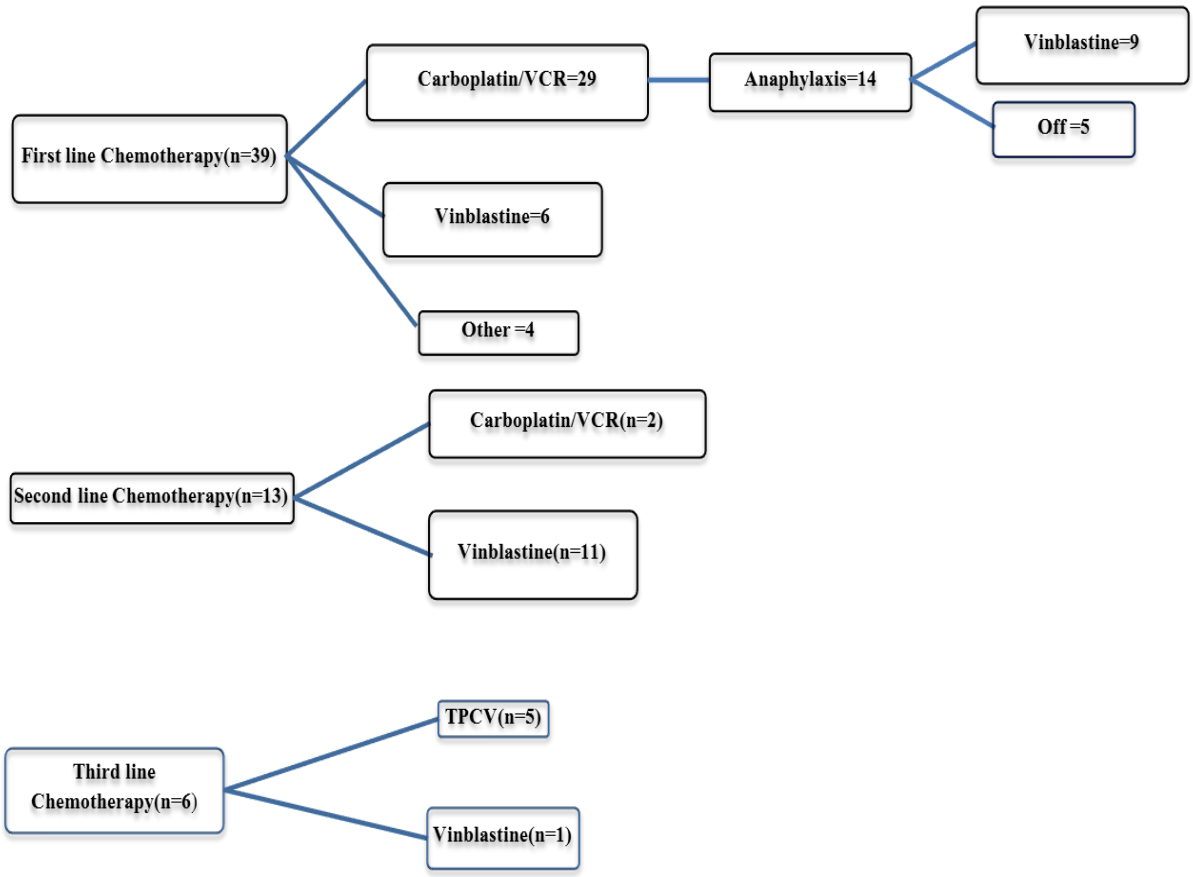

Figure 1. chemotherapy regimen details

Radiotherapy

Only 6 patients received radiotherapy during their disease course; 3 had their tumors at the cerebrum; the other 3 patients had their disease at the pineal, cervicomedullary, and posterior fossa/cerebellar sites subsequently (table 3).

Table 3. details of patients received radiotherapy

Gender/ Age (yr)	Location	Treatment	Pathology Diagnosis	Age at Treatment	outcome
M/13.9	Cerebrum	GTR/NO chemo	pilocytic astrocytoma	14 yr	No evidence of disease
F/6.3	Pineal	PR/Carbo-VCR(2cycles)	pilocytic astrocytoma	7 yr	AWD
M/17.1	Cerebrum	GTR/TMZ	fibrillary astrocytoma	17.1 yr	No evidence of disease
M/6	Cerebrum	3 STR/TMZ	DIG→Anaplastic	10 yr	Died
F/4	cervicomedullary	STR/VBL/Carbo-VCR	ganglioglioma	4 yr	AWD
F/2.9	posterior fossa/ Cerebellum	PR/TMZ	pilocytic astrocytoma	3 yr	AWD

M, male; F, female; GTR, gross total resection; STR, subtotal resection; PR, partial resection; Carbo, VCR, carboplatin/vincristine; TMZ, temozolamide; VBL, vinblastine; DIG, desmoplastic infantile ganglioglioma; AWD, alive with disease

Outcomes: total and by risk stratification

Until writing this study, nineteen patients have no evidence of the disease, 61 are alive with disease, and 5 patients died. The

5-year PFS rate for patients was 60% ±7.3% (Figure 2A), and the 5-year OS rate was 92% ± 4.1% (Figure 2B). The 5-year PFS rate according to site of the tumor was as follows: spinal, 100%; cervicomedullary, 100%; posterior fossa/ cerebellum, 95%;optic nerve, 75%; cerebrum, 68%; pineal, 50%; suprasellar/ hypothalamic, 31%; thalamic, 25%; this difference was significant (*P*=0.048) (Figure 3 A).

The 5-year PFS according to the degree of resection after the 1st surgery was as follows: GTR, 100%; STR, 49%; biopsy/PR, 45%; there was a significant statistical difference according to the extension of surgery (*P*=0.023) (Figure 3 B). there was no significant statistical value of the 5-year EFS according to the type of chemotherapy given (*P*=0.57) (Figure 3 C).

Discussion

Management of pediatric LGG in developing countries is still not well established; the cornerstone of the treatment in those countries is the surgery followed by radiotherapy without awareness of its late sequel and adverse effects especially in a growing brain of the child [4].

In this study, we report the outcomes of children with LGG in a single institution in Jordan. At King Hussein Cancer Center (KHCC), 70% of patients are Jordanians who get full financial coverage through the Ministry of Health. The non-Jordanian patients are either supported by referring hospitals outside Jordan or receive donations from the charity foundation (King Hussein Cancer Foundation).

Although there was a higher male/female ratio in this study, this does not reflect the referral pattern at our institution. A multidisciplinary team comprising of pediatric oncologists, pediatric neurosurgeons, radiation oncologists, radiologists, pathologists, and psycho-social team was formed in 2006 and meets once weekly to discuss the care of children with central nervous system tumors.

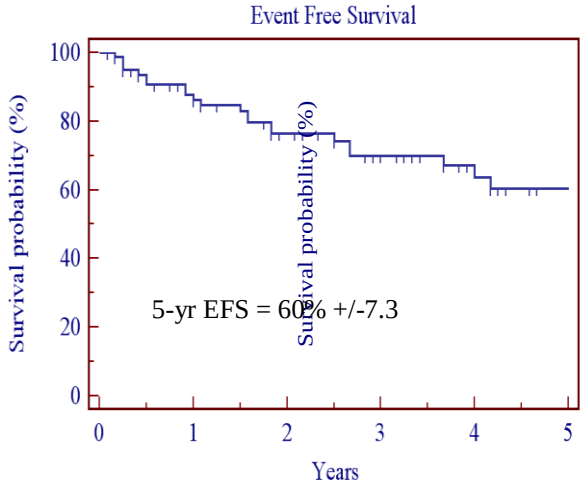

Figure 2 A

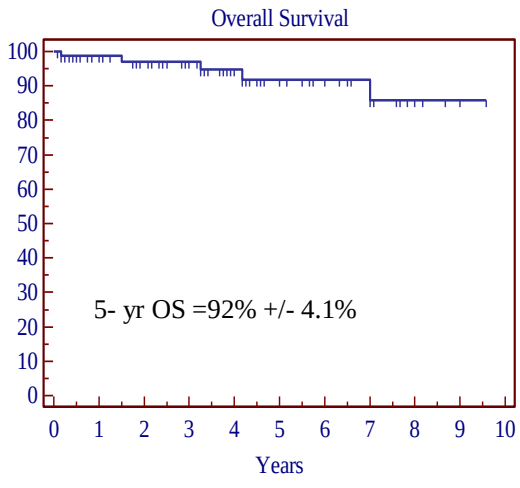

Figure 2 B

Figure 2. five-year event free survival (EFS) (2 A) and overall survival (OS) (2 B) rate

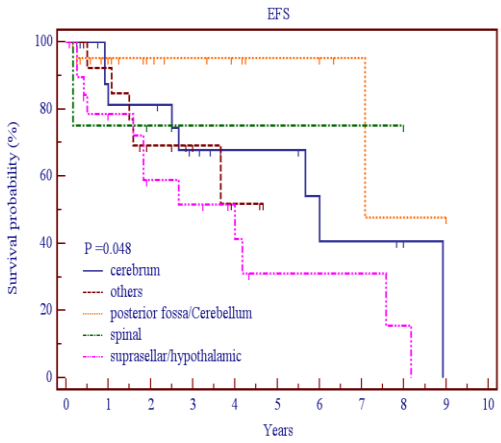

Figure 3 A

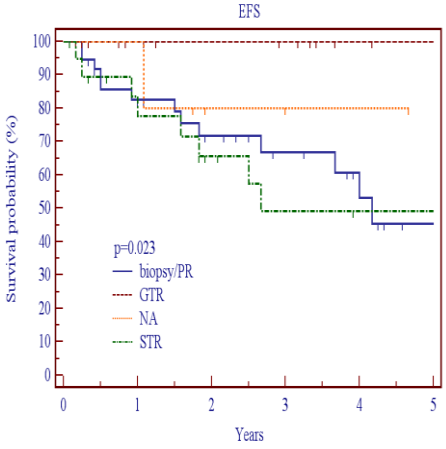

Figure 3 B

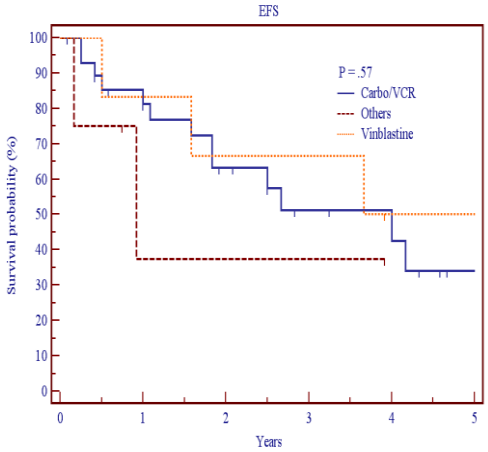

Figure 3 C

Figure 3. Event free survival (EFS) according to the site of the disease (3 A), extent of the first surgical resection (3 B), and the type of chemotherapy given (3 C)

Table 4. Five year event-free survival (EFS) according to the tumor location (A) and extent of surgical resection (B)

(A)

Location	**5-yr EFS**
Cerebrum	68 +12
Posterior fossa/cerebellum	95 +4.7
Spinal	100
Suprasellar/hypothalamic	31 +14
Cervicomedullary	100
Pineal	50 + 35
Thalamic	25 +21
Optic nerve	75 + 22

(B)

Surgery	**5-yr EFS**
GTR	100
STR	49 +/- 13
PR/Biopsy	45 +/- 12

As there is a growing gap between developing and developed countries in the availability of treatment for pediatric subspecialties, and there is an evidence that twining and telemedicine with the developed countries are effective ways to improve the quality of healthcare in developing countries [15-17], our results may reflect the impact of this twining and telemedicine on the management and care of children with LGG.

In this study, the 5-year EFS was (60% ± 7.3%) and the OS was (92 ± 4.1%), which were almost similar to those reported previously in the literature by Fisher et al and Gnekow et al [18, 19]; this may reflect

the useful impact of telemedicine-based twining program between the KHCC, and the Hospital for Sick Children, Toronto, Canada, on the improvement of survival of children with cancer in developing countries puplished by Qaddoumi et al [16].

There was a significant association between the EFS rate and the site of the disease as well as the extent of the 1st surgical resection; by this, we confirmed prior reports that hemispheric and cerebellar tumor location and the greater extent of resection, particularly GTR, predict improved survival [20-25].

Chemotherapy is a valid alternative modality of treatment to radiation in the management of nonresectable pediatric LGG; preliminary results have suggested that chemotherapy can delay or even allow avoidance of the use of radiation in a significant proportion of children [8, 13, 26-29]; several chemotherapy regimens have been used, but the choice of the optimal regimen is still a matter of debate. Our relatively large sample provided a unique opportunity to evaluate the effect of replacement of radiotherapy by chemotherapy on the natural course of LGG in developing countries.

In this study, there was no significant statistical difference between the EFS and the regimen of chemotherapy given; this may indicate that using any kind of chemotherapy regimen may have a similar effect in delaying or avoiding the use of radiotherapy.

Carboplatin/vincristine combination chemotherapy may have some superiority preference over other regimens relating to its attractive minimal long- term toxicity [27]; however, the higher rate of hypersensitivity reaction (HSR) may lead to early cessation of this chemotherapy regimen; our results showed that 14 out of 31 cases (45.1%) developed HSR, which is almost similar to that reported from developed countries by Lafay-Cousin et al [30].

Conclusion

LGG are chronic illnesses that require close follow up and repeated interventions, with high cost and major impact on the family; their management in developing countries can be improved through a multidisciplinary approach; The main impact of this approach was the elimination of radiotherapy from the management of most patients with LGG in our center.

The role of telemedicine in this experience was significant in providing suggestions and helping the decisions.

References

1. Campbell JW, Pollack IF. Cerebellar astrocytomas in children. J Neurooncol. 1996 May-Jun;28:223-31. Epub 1996/05/01. eng.
2. Kreth FW, Warnke PC, Ostertag CB, Berger MS, Deliganis AV, Dobbins J, et al. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer. 1995 Jun 1 Sep 15;75:2785-7. PubMed PMID: 7743491. Epub 1995/06/01 1994/09/15. eng.
3. Palma L, Guidetti B. Cystic pilocytic astrocytomas of the cerebral hemispheres. Surgical experience with 51 cases and long-term results. J Neurosurg. 1985 Jun;62:811-5. Epub 1985/06/01. eng.
4. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009 Aug 1;27:3691-7. PubMed PMID: 19581535. Pubmed Central PMCID: 2799064.
5. Castello MA, Schiavetti A, Varrasso G, Clerico A, Cappelli C. Chemotherapy in low-grade astrocytoma management. Childs Nerv Syst. 1998 Jan-Feb;14:6-9. Epub 1998/04/21. eng.
6. Petronio J, Edwards MS, Prados M, Freyberger S, Rabbitt J, Silver P, et al. Management of chiasmal and hypothalamic gliomas of infancy and childhood with chemotherapy. J Neurosurg. 1991 May;74:701-8. Epub 1991/05/01. eng.
7. Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA. Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neurooncol. 1997 May;32:235-41. Epub 1997/05/01. eng.

8. Lafay-Cousin L, Holm S, Qaddoumi I, Nicolin G, Bartels U, Tabori U, et al. Weekly vinblastine in pediatric low-grade glioma patients with carboplatin allergic reaction. Cancer. 2005 Jun 15;103:2636-42. PubMed PMID: 15861409.
9. Perry A. Pathology of low-grade gliomas: an update of emerging concepts. Neuro-oncology. 2003 Jul;5:168-78. PubMed PMID: 12816723. Pubmed Central PMCID: 1920686.
10. Sawamura Y, Kamada K, Kamoshima Y, Yamaguchi S, Tajima T, Tsubaki J, et al. Role of surgery for optic pathway/hypothalamic astrocytomas in children. Neuro-oncology. 2008 Oct;10:725-33. PubMed PMID: 18612049. Pubmed Central PMCID: 2666249.
11. Gnekow AK, Kaatsch P, Kortmann R, Wiestler OD. [HIT-LGG: effectiveness of carboplatin-vincristine in progressive low-grade gliomas of childhood--an interim report]. Klinische Padiatrie. 2000 Jul-Aug;212:177-84. PubMed PMID: 10994547. HIT-LGG: Effektivitat von Carboplatin-Vincristin bei progredienten Gliomen niedrigen Malignitatsgrades im Kindesalter--Zwischenbericht.
12. Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 Apr 20;30:1358-63. PubMed PMID: 22393086.
13. Massimino M, Spreafico F, Cefalo G, Riccardi R, Tesoro-Tess JD, Gandola L, et al. High response rate to cisplatin/etoposide regimen in childhood low-grade glioma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002 Oct 15;20:4209-16. PubMed PMID: 12377964.
14. Ater JL, Zhou T, Holmes E, Mazewski CM, Booth TN, Freyer DR, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 Jul 20;30:2641-7. PubMed PMID: 22665535. Pubmed Central PMCID: 3413276.
15. Qaddoumi I, Bouffet E. Supplementation of a successful pediatric neuro-oncology telemedicine-based twinning program by e-mails. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. 2009 Dec;15:975-82. PubMed PMID: 19929233.
16. Qaddoumi I, Mansour A, Musharbash A, Drake J, Swaidan M, Tihan T, et al. Impact of telemedicine on pediatric neuro-oncology in a developing country: the Jordanian-Canadian experience. Pediatric blood & cancer. 2007 Jan;48:39-43. PubMed PMID: 17066456.
17. Sable CA, Cummings SD, Pearson GD, Schratz LM, Cross RC, Quivers ES, et al. Impact of telemedicine on the practice of pediatric cardiology in community hospitals. Pediatrics. 2002 Jan;109E3. PubMed PMID: 11773571.
18. Fisher PG, Tihan T, Goldthwaite PT, Wharam MD, Carson BS, Weingart JD, et al. Outcome analysis of childhood low-grade astrocytomas. Pediatric blood & cancer. 2008 Aug;51:245-50. PubMed PMID: 18386785.
19. Gnekow AK, Falkenstein F, von Hornstein S, Zwiener I, Berkefeld S, Bison B, et al. Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro-oncology. 2012 Oct;14:1265-84. PubMed PMID: 22942186. Pubmed Central PMCID: 3452343.
20. Due-Tonnessen BJ, Lundar T, Egge A, Scheie D. Neurosurgical treatment of low-grade cerebellar astrocytoma in children and adolescents: a single consecutive institutional series of 100 patients. Journal of neurosurgery Pediatrics. 2013 Mar;11:245-9. PubMed PMID: 23240848.
21. Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA. Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery. 2008 Dec;24:1447-55. PubMed PMID: 18690461.
22. Berger MS, Deliganis AV, Dobbins J, Keles GE. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer. 1994 Sep 15;74(6):1784-91. PubMed PMID: 8082081.
23. Kreth FW, Warnke PC, Ostertag CB. Low grade supratentorial astrocytomas: management and prognostic factors. Cancer. 1994 Dec 15;74(12):3247-8. PubMed PMID: 7982190.
24. Pollack IF, Claassen D, al-Shboul Q, Janosky JE, Deutsch M. Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. Journal of neurosurgery. 1995 Apr;82(4):536-47. PubMed PMID: 7897512.
25. Piepmeier J, Christopher S, Spencer D, Byrne T, Kim J, Knisel JP, et al. Variations in the natural history and survival of patients with supratentorial low-grade astrocytomas.

Neurosurgery. 1996 May;38(5):872-8; discussion 8-9. PubMed PMID: 8727811.
26. Moschovi M, Alexiou GA, Papakonstantopoulou I, Gavra M, Sfakianos G, Prodromou N. Efficacy of carboplatin plus vincristine in an optic pathway glioma. Klinische Padiatrie. 2010 Nov;222(6):395-6. PubMed PMID: 20806167.
27. Packer RJ, Lange B, Ater J, Nicholson HS, Allen J, Walker R, et al. Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1993 May;11:850-6. PubMed PMID: 8487049.
28. Packer RJ, Ater J, Allen J, Phillips P, Geyer R, Nicholson HS, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. Journal of neurosurgery. 1997 May;86:747-54. PubMed PMID: 9126887.
29. Gajjar A, Heideman RL, Kovnar EH, Langston JA, Sanford RA, Douglass EC, et al. Response of pediatric low grade gliomas to chemotherapy. Pediatric neurosurgery. 1993 May-Jun;19:113-8; discussion 9-20. PubMed PMID: 8499323.
30. Lafay-Cousin L, Sung L, Carret AS, Hukin J, Wilson B, Johnston DL, et al. Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. Cancer. 2008 Feb 15;112:892-9. PubMed PMID: 18098210.