Quality of Life in Patients with Skull Base Tumors: Current Status and Future Challenges

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ABSTRACT

In selection of the right treatment for a specific patient, the surgeon should consider not only the best approach to remove a tumor but also the impact of treatment on the quality of life (QOL) of the patient. Procedures involving extirpation of skull base tumors may be associated with high morbidity. It is therefore important to study patients with skull base neoplasms, because survival differences between various treatment modalities may be small, yet larger differences are expected regarding morbidity. The overall QOL in the majority of patients after skull base tumor resection can be classified as “good,” with significant improvement taking place within 12 months following surgery. Patients with carcinomas, acoustic schwannoma, or Cushing’s disease suffer from more significant deterioration in their QOL after any intervention. Data retrieved from disease-specific questionnaires revealed that the financial and emotional domains have the worse impact on patients QOL. Old age, malignancy, comorbidity, radiotherapy, and extensive surgery were found to be also negative prognostic factors for QOL. Pain control regimens, antidepressants, and other psychological modalities, including group support, can improve QOL measures in these patients. It is critical that surgeons understand that they cannot assess their patients’ perspectives on QOL correctly without asking them. For adequate assessment, validated disease-specific instruments addressing multiple domains of QOL should be utilized.

KEYWORDS: Quality of life, cranial base, craniofacial, cancer, neurosurgery

Tumors involving the skull base represent a group of different histologies with distinct clinical implications. Recent improvements in surgical techniques now allow safe resection of these tumors with acceptable morbidity. In the past, studies of skull base neoplasms (SBNs) have focused on traditional end points, such as completeness of tumor removal, response to radiation, survival, and local control. More recently, investigators

have begun to appreciate the importance of quality of life (QOL) outcomes, particularly in the setting of skull base surgery in which patients and surgeons now acknowledge the importance of considering not only the impact of treatment on survival but also the well-being of the patient following surgery. This is particularly relevant for patients with SBNs because the treatments for these tumors typically involve extensive surgery, with or

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without adjuvant radiation therapy, which can have devastating morbidity and toxicity.

QOL studies are particularly challenging in these patients for several reasons: (1) many of them are elderly patients with multiple comorbidities, (2) short-term survival and deteriorated general status complicate data collection, and (3) the small number of patients and histological variability make QOL analysis more difficult than in other head and neck cancers. It is critical that surgeons understand that they cannot assess their patients' perspectives on QOL issues without asking them¹ and that validated disease-specific instruments addressing multiple domains of QOL should be utilized for adequate assessment.²

In this article, we review the results of pioneering QOL studies in the field of skull base surgery and discuss the use of QOL assessment in the clinic and in clinical trials.

WHY SHOULD SURGEONS MEASURE PATIENTS' QOL?

The technical development of skull base surgery has had a major positive impact on the long-term survival of patients with lesions involving the cranial fossa.³ Although surgical procedures are crucial for treatment of SBNs, tumor control should not be the only goal of patient care. It is therefore commonly accepted that the two main goals of treatment are to improve survival and to quickly restore patients' QOL. QOL is defined as a patient's subjective view of his current physical, psychological, and social well-being compared with what he perceives to be possible or ideal. By assessing patients' QOL, the physician can gain multiple objectives (Table 1). Estimation of the influence of surgical procedures on QOL can serve as a means by which the most appropriate surgical approach can be selected for a given patient. For example, information on QOL is required to decide whether a specific treatment is associated with a better impact on patients' well-being than other procedures. Detailed understanding of the different

aspects of QOL may help surgeons improve assessment and management of patients, identify specific impediments as early as possible during follow-up, and apply appropriate medical interventions to patients with increased risk and poor outcome. Furthermore, early access of patients to detailed information about their disease can lead to better adjustment to an imminent medical condition. A multidimensional evaluation of QOL involves retrieving information on the physical, emotional, social, and economic aspects of the patients' lifestyles, as well as on specific symptoms associated with their disease (Fig. 1). Valid interpretation of the data requires generic questionnaires or disease-specific instruments, which cover the morbidity associated with the site of cancer and its treatment. Using these types of instruments allows the directing of support endeavors to the most critical issues that may affect a patient's rehabilitation. Another reason to study QOL is related to our ability to predict patients' outcome and survival by means of pretreatment QOL questionnaires.^{4,5} Using a simple Karnofsky scale for patients undergoing surgery for anterior skull base cancers, we found a highly significant correlation between the K score and survival (Gil et al, unpublished data): the overall 5-year survival of patients with Karnofsky scores >70 was 56 months compared with 23 months in patients with scores <70 ($p < 0.0001$). Although the Karnofsky score is not considered a reliable estimate of QOL, our data and those of other studies suggest that the preoperative estimation of a patient's function in his or her daily life may serve as an indicator of outcome. An instrument for assessment of functional domains would be a valuable adjunct for individualization of treatment, especially in patients with SBNs.

Table 1 Objectives for Estimating Patient's Quality of Life

Objectives
Estimation of outcome
Improving physician-patient communication
Identification of specific impediments during and after treatment
Monitoring of patient care
Facilitate restoration of functioning
Application of specific medical interventions
Improving treatment modalities
Interpretation of clinical trials
Improving adjustment to a new status
Understanding patients' expectation from treatment

Figure 1 Domains of quality of life.

WHAT IS THE IMPACT OF QOL ASSESSMENTS ON DAILY CLINICAL PRACTICE?

In the absence of level I evidence, decisions regarding management of patients with skull base tumors are guided by numerous factors, including the surgeon's preferences, routine hospital practices, availability of equipment, and input from other team members. The time available to the surgeon for routine postoperative follow-up visits is usually limited. Repeated measurements of the patients' overall condition as well as monitoring the effect of pain and psychiatric medications can be easily performed with short QOL instruments that can be completed in the clinic on regular bases. These results can be used by the multidisciplinary team to adjust supportive treatment modalities and to guide social and psychiatric interventions to a selected population of patients who may highly benefit from them.

WHY MEASURE QOL IN CLINICAL STUDIES?

The benefit of QOL assessment as a research tool is well established. In 1988, the National Cancer Institute declared in its mission statement that research at improving QOL for patients with cancer is of the highest priority (Clinical Trials Cooperative Group Program, 1988). As demonstrated in other surgical fields, QOL assessment can illustrate the benefit of treatment modalities that have similar oncologic results.⁶ For example, it can facilitate decision making of which subpopulation of patients with skull base schwannomas is likely to exhibit better QOL after treatment with primary radiotherapy rather than surgery. Differences in patterns of personality traits, coping mechanisms, and socioeconomic features along with preexisting medical factors can contribute to a qualitatively and quantitatively superior QOL. Indeed, QOL data can sometimes provide an unexpected result. For example, the question of whether endoscopic approaches with their potential for causing permanent nasal morbidity are advantageous over frontal craniotomy for skull base meningiomas awaits scientific proof. Without such level of evidence, one cannot assume a superiority of one surgical procedure over the other. For these reasons, QOL assessments should be included as regular criteria for assessing the success of treatment in patients with SBNs, especially when the treatment modality is newly introduced.

HOW SHOULD QOL BE MEASURED IN SKULL BASE PATIENTS?

There is no doubt that QOL is an important end point that should be incorporated into clinical studies of

patients with SBNs. The question is how QOL of skull base patients should be assessed? Site-specific modules incorporating questions addressing disease- and treatment-specific problems have been developed based on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for the head and neck. The head and neck module of the EORTC includes questions on swallowing, breathing, and mastication, but these issues are not relevant to patients with skull base neoplasms, and the absence of questions that are related to the specific symptoms of patients with skull base tumors limits the application of these instruments in skull base surgery. The QOL instrument predominantly used in anterior skull base surgery is the Anterior Skull Base Questionnaire (ASBQ).¹ This questionnaire, which was established in 2003, is a disease-specific instrument based on a pooling of questions related to general QOL and to head and neck cancer. Questions were later added to this instrument to cover symptoms specifically associated with anterior skull base tumors and postoperative morbidity. These questions were generated from interviews with health professionals and surgeons as well as from interviews with patients and their caregivers. They cover problems on various aspects of taste, smell, appearance, nasal function, and visual function, which are frequently found in this population. A recent prospective study further established the ASBQ as the main instrument for evaluating QOL of patients with anterior skull base tumors and demonstrated its ability to predict the QOL of different groups of patients even prior to surgery⁷ (see also Abergel et al in this issue). This questionnaire is available in English, Portuguese, Italian, Hebrew, and Swedish and will be incorporated into the 2009 international collaborative study on anterior skull base tumors (see article by Patel in this issue). Translation to other languages is underway.

QOL OF PATIENTS WITH ANTERIOR SKULL BASE NEOPLASMS

The evaluation of QOL in patients with anterior skull base tumors is particularly challenging for several reasons. First, many of these patients have intracranial extension of their tumor (i.e., patients who are at risk of brain injury during surgery and subsequently to postoperative cognitive dysfunction). Second, management of these patients requires extensive surgical intervention, prolonged hospitalization, and long periods of rehabilitation. Finally, many of these patients require additional surgeries and adjuvant treatment. Issues that may influence the functional outcome of patients are anosmia, hearing loss, meningitis, cerebrospinal fluid leak, osteoradionecrosis and fistula, impaired nasal function, cosmesis, and visual disturbances. In an early study, Janecka

et al used the Karnofsky performance score to evaluate the effect of cranial base surgery on patients' QOL.⁸ They showed that 83% of these patients had improved or unchanged scores after surgery. The long-term QOL of patients undergoing anterior skull base tumor resection was recently assessed using a disease-specific instrument.^{1,2,9} These results showed that 38% of the patients reported a significant improvement in overall QOL, 36% reported no change in QOL, and 26% responded that the surgical procedure worsened their QOL. In addition, there was improvement in QOL measures at 6 to 24 months following surgery and stability of the scores within 6 months after surgery. Fukuda et al¹⁰ evaluated 13 patients with anterior skull base tumors who underwent classical craniofacial resection for malignant tumors; eight patients reported that their QOL worsened after surgery.

Studies on patients with malignant intracranial tumors have demonstrated severely deteriorating QOL measures, with marked decline in cognitive, physical, emotional, and social functioning after surgery.¹¹ Similarly, one QOL analysis of 18 patients with carcinomas of the paranasal sinuses showed that the worst affected domains were mood, anxiety, and activity.¹² Patients with anterior skull base cancer had poorer QOL scores than those with lateral skull base malignancy.

QOL IN PATIENTS WITH SKULL BASE MENINGIOMAS

Mohsenipour et al¹³ recently showed that the majority of patients after meningioma resection had mild to moderate impairment in overall QOL, but that there was severe impairment in the physical handicap and energy level domains. Similar results were reported for meningiomas involving the cavernous sinus.¹⁴ In another study that looked at the outcome of 105 patients after excision of petroclival meningioma in which a standard lateral skull base approach was used,¹⁵ 76% of the patients reported good to moderate recovery at 1 year postoperatively, but 39 to 72% of these patients were still functioning below accepted norms.

The stability of QOL following surgery is an important issue of patients' overall QOL and quality of recovery. A temporal evaluation of QOL after anterior skull base surgery and excision of meningiomas involving the cavernous sinus showed a gradual improvement of QOL measures during the first year after surgery and stability of scores during the second year. Gradual deterioration of QOL, however, was observed during the postoperative period among patients with intracranial tumors. Old age was associated with a negative impact on health-related QOL following resection of anterior skull base tumors or cavernous sinus meningiomas.^{13,15}

QOL IN PATIENTS WITH ACOUSTIC SCHWANNOMA

Estimation of health-related QOL is particularly important in patients with acoustic schwannoma. Nikolopoulos et al¹⁶ used the Glasgow Benefit Inventory for evaluating a patient's QOL after resection of acoustic schwannoma: more than 50% of their 53 patients reported an overall decline in QOL. In addition, one-third of their patients had declined financial status as a consequence of the operation. Tufarelli et al¹⁷ used both the Medical Outcome Study 36-Item Short Form and Dizziness Handicap Inventory and found significant deterioration of QOL among females and patients >45 years of age. Similar results were reported by da Cruz et al¹⁸ for the translabyrinthine and retrosigmoid approaches and by Baumann et al¹⁹ for the middle cranial fossa approach. In contrast, Irving et al²⁰ used the EORTC instrument to show an excellent QOL after resection of acoustic schwannomas, especially for tumors smaller than 1.5 cm. An interesting study performed by Myrseth et al²¹ evaluated the QOL of patients treated for unilateral vestibular schwannoma by microsurgery or by gamma knife radiosurgery. The QOL, posttreatment facial nerve function, and hearing were significantly better in the radiosurgery group, and improved QOL scores were associated with better facial nerve and hearing function. In contrast, Sandooram et al²² suggested that a conservative management approach consisting of watchful waiting is associated with a better QOL outcome compared with both radiosurgery and microsurgery.

In the largest study performed to date, Ryzenman et al²³ used a disease-specific questionnaire and demonstrated that low QOL scores were specifically associated with postoperative headache symptoms after excision of schwannomas. A similar result was reported by Betchen et al using generic instruments.²⁴ Young patients had a worse overall QOL and financial status compared with older patients after excision of acoustic neuromas. A negative impact of surgery on patients with acoustic schwannoma, especially in the young population, is expected as their preoperative health-related QOL is hardly affected by their disease, particularly when the tumor is small.

QOL OF PATIENTS WITH SKULL BASE PARANGLIOMAS

There is considerable debate in the field of skull base surgery on the management of patients with paragangliomas involving the skull base. The options of treatment for this population are watchful waiting, surgery, or radiation therapy. Surgery in this anatomic area can involve significant morbidity that may have considerable effect on patients' functional outcome. Because multiple cranial nerves deficits, particularly in large tumors, are of

significant concern, the benefit of treatment should also be judged by the potential functional outcome after surgery. The impact of surgery for skull base paragangliomas on QOL was reviewed by Briner and his colleagues.²⁵ Most of their patients (98%) returned to their previous occupations within 2 years after surgery, but only 75% returned to their preoperative baseline QOL levels. The most important subjective sequelae of surgery were swallowing difficulties, impaired facial function, headache, and hearing loss. As expected, patients with intracranial extension had the most significant deteriorated functional outcome.²⁵

QOL OF PATIENTS WITH PITUITARY ADENOMAS

The impact of pituitary adenomas on the QOL of patients was studied extensively during the last decade. Disturbed mood disorders and deteriorated cognitive function noted by early studies reportedly contributed to a deteriorated QOL scores in this population.^{26,27} Cognitive impairment was more severe after transfrontal surgery, most likely due to frontal lobe retraction and encephalomalacia.²⁸⁻³⁰ A subpopulation of patients with Cushing's disease continued to experience substantial problems in multiple domains of QOL for several years after surgery, even when apparently "biochemically" cured.³¹ Glucocorticoid supplementation had little effect on long-term QOL outcomes.³²

An excellent example of the utility of QOL in the skull base literature can be found in new studies on patients undergoing a transfrontal versus a transsphenoidal approach for pituitary adenoma. Several studies concluded that patients who undergo transfrontal surgery have a poorer outcome in terms of psychological well-being than patients surgically treated transsphenoidally.^{31,33} Although these results may have involved selection bias, it is one of the reasons that the transsphenoidal approach gained popularity over more traditional approaches during the last few decades.³⁴ It was also believed that patients receiving adjuvant radiotherapy performed worse than those receiving only surgery, especially in the cognitive and role of function domains.³⁴ However, a recent comparative study on patients with nonsecreting pituitary adenomas undergoing surgery with or without radiotherapy showed no difference in QOL and cognitive function between the groups.³⁵

LONG-TERM QOL IN CHILDREN AND ADULTS WITH CRANIOPHARYNGIOMA

Surgical resection of craniopharyngioma is associated with morbidity of multiple systems, such as pituitary insufficiency, visual field defects, and a high incidence of cardiovascular risk factors.³⁶⁻³⁸ Patients undergoing sur-

gery and radiotherapy for craniopharyngioma also have a decreased QOL despite long-term hormonal replacement therapy. Contributors to a deteriorated QOL in this population include poor performance scores, fatigue, pain, and changes in emotional status.³⁹ Significant predictors for deteriorated QOL scores are visual field defects, female gender, recurrent operation, and radiation therapy.³⁹ A reduction in long-term QOL was also reported in children operated for craniopharyngioma.^{40,41} The domains of social and emotional functioning were particularly affected in this age group.⁴² Interestingly, the scores reported by parents were significantly lower than those reported by the children.⁴² Large tumors, displacement of the hypothalamus, hydrocephalus, multiple surgeries, and young age at diagnosis were associated with poor QOL scores. Comparative assessment of QOL in patients with craniopharyngioma revealed no significant difference between adult- and childhood-onset craniopharyngioma.³⁷

HOW CAN PATIENTS' QOL BE IMPROVED?

As physicians, we are trained to give our patients the optimal treatment for achieving the highest survival rate. Managing patients' QOL is often shadowed by the possibility for a cure. Although increasing efforts have been made to develop new surgical approaches and novel adjuvant modalities for the treatment of cancer during the last century, little progress has been made in developing new techniques for improving patients' QOL. How, then, can we improve patients' QOL after resection of skull base tumors? One way to positively affect their postoperative QOL involves pain control. Skull base procedures are associated with a considerable level of pain during the early postoperative period.⁴³ Although many analgesic regimens are available (e.g., as needed, scheduled dosing, intravenous patient-controlled intravenous analgesia), little is known about the optimal therapeutic modality for the treatment of acute postoperative pain after skull base procedures. In a multidepartmental survey of acute pain level measured following surgery, the neurosurgical and craniofacial-related pain was rated 5 and 7 out of 11, respectively, making it less than orthopedic, abdominal, gynecologic, and urologic procedures and greater than plastic, ophthalmologic, vascular, and oral procedures.⁴⁴ In a recent study, Gil et al⁴³ estimated the level of pain following skull base surgery and used their data to tailor a specific pain control protocol specific to each procedure. The overall results of that study showed that an as needed protocol is not adequate for the management of pain following skull base surgery. Those patients most frequently required continuous drainage of cerebrospinal fluid due to violation of the dura during surgery, and this mandates bed rest for 5 days until the drain is removed. They complained mainly of musculoskeletal and back

pain as a result of lying in a supine position for a prolonged period of time. Pain control medication is recommended for these patients whether or not they request painkillers.

One approach to meet the demands of patients and to best utilize resources is the use of a multidisciplinary team approach to provide better care, compared with an individual patient–physician care protocol. When properly implemented, this team approach provides positive measurable outcomes. A multidisciplinary team can provide more comprehensive care than an individual patient–surgeon approach and so enhance the patient's QOL. The management scheme should also include patient satisfaction and QOL questionnaires, self-management brochures, employment of a community support network, scheduled follow-up, and use of database information systems. Medical and paramedical support should also involve practical, informational, and emotional support. Screening patients for psychosocial distress can be conducted quickly via a QOL questionnaire and is important for identifying patients requiring additional interventions. The main efforts to improve QOL should focus on subgroups of patients who are at highest risk to suffer significant impairment of their QOL (i.e., the elderly and patients with malignant disease, comorbidity, or recurrent disease). Psychosocial barriers and family issues are also key factors in determining QOL. The role of the health care professionals who are part of the multidisciplinary team is to address short-term complications as a result of surgical or adjuvant therapy and to provide appropriate monitoring of long-term complications for early detection of depression or financial problems. Sources of assistance can be accessed by telephone, e-mail, and dedicated Web sites, and they can include support groups, specialists who answer questions online and on Weblogs (blogs).

Up to two-thirds of patients with cancer may suffer from depression, with half of them having at least one episode of major depression.⁴⁵ Pharmacological treatment was shown to induce significant improvement in depression symptoms within 6 weeks after administration of antidepressant therapy.^{46,47} Psychotherapeutic cognitive and behavioral therapies had an impact on the level of depression and symptoms in patients with cancer, and combined behavioral and pharmacological therapy was shown to even further reduce the level of depression in these patients.^{48,49} Psychological intervention by means of group support has been shown not only to increase QOL, but also to provide survival benefit for patients with metastatic carcinoma.⁵⁰ Other studies have established the benefit of psychological group support in patients with other malignancies.^{51,52} A module of psychological group support can include 5 to 10 patients with similar disease conditions and two leaders. The leaders should include one member of the surgical team and one member of the nursing team, along with a

psychiatrist, a psychologist, or a social worker who is experienced in leading group support therapy.⁵³ Group support may include discussions on a patient's relationships with family, friends, and the health caregivers, the effect of the disease on a patient's daily lifestyle, and past and future treatment modalities. Another way of decreasing patients' distress is by introduction to and discussion with cancer survivors who had been treated by the same multidisciplinary team. Patients may also be trained to practice relaxation exercises during each seminar and at home with or without the aid of a spouse or health caregiver. Finally, a Web-based social support group can also be effective in reducing depressive symptoms in cancer patients.⁵⁴

FUTURE CHALLENGES

During the last decade, most clinical studies on patients with SBNs typically reported on the surgical technique, complications, and survival. Estimation of the well-being of the patients usually focused on their Karnofsky score. These studies were important to provide clinical information on the feasibility and safety of complicated skull base operations and to establish the optimal surgical techniques. Our next goal should also be directed toward improving our understanding of the impact of surgery, radiation, and chemotherapy on the QOL of the patients, and toward developing means to improve it. The current challenge in skull base surgery is to advance QOL research, including the conducting of comparative studies of multiple treatment regimens with similar survival end point measures. Finally, QOL research in patients with skull base tumors will ultimately advance our efforts to improve their life expectancy and afford them a normal way of life.

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