Assessing Quality of Life among Radiation-Induced Hypopituitary Patients

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Abstract

Introduction Radiation-induced hypopituitarism (RIH) has long been recognized as one of the deleterious side effects of skull base radiation. This study aims to assess the quality of life (QoL) among patients with RIH compared with radiated patients who did not develop hypopituitarism using the validated Anterior Skull Base Questionnaire (ASBQ).

Methods This was a single-institution retrospective cohort study. Included patients had a history of anterior skull base tumor, underwent at least one round of radiation to the skull base, and had filled out at least one ASBQ survey after their radiation treatment. Three statistical models were used to determine the effect of hypopituitarism and treatment on QoL scores.

Results A total of 145 patients met inclusion criteria, and 330 ASBQ surveys were analyzed. Thirty-five percent (51/145) had evidence of RIH at some point after their radiation treatment. Those with hypopituitarism had significantly lower overall ASBQ scores across all three models even after adjusting for potential confounders and intraperson correlation (average decrease of 0.24–0.45 on a 5-point Likert scale; *p*-values ranging from 0.0004 to 0.018). The increase in QoL with hormonal replacement was modulated by time out from radiation, with long-term survivors (5+ years out from radiation) gaining the most benefit from treatment (increase of 0.89 on a 5-point Likert scale, *p* 0.0412), especially in the vitality domain.

Conclusion This data demonstrates that hypopituitarism is an independent predictor of lower QoL. Early detection and appropriate treatment are essential to avoid the negative impact of hypopituitarism on QoL.

Keywords
- sinonasal malignancies
- radiation side effects
- radiation-induced hypopituitarism
- hypopituitarism screening
- quality of life
- Anterior Skull Base Questionnaire

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Introduction

Radiotherapy is a mainstay of definitive or adjuvant treatment for anterior skull base tumors. Radiation-induced hypopituitarism (RIH) has long been recognized as one of the deleterious side effects of skull base radiation. RIH can present within the first few years to as late as 20 years after radiation.[1] RIH not only occurs in patients who received direct sellar radiation but also to patients with nearby tumors, as the hypothalamic-pituitary unit commonly falls within the radiation field.[1] These tumors include cranial tumors not involving the hypothalamic-pituitary-axis (HPA) and even oropharyngeal tumors whose radiation field include the sella.[2,3] Higher radiation doses (greater than 50 Gy), as commonly seen for anterior skull base malignancies and nasopharyngeal carcinoma, are associated with higher incidence of HPA dysfunction.[1,4–6] The estimated cumulative incidence of RIH after high-dose radiation is broad, with estimates ranging from 37% over 3 years among our own institutional cohort of sinonasal malignancies,[5] to 41% at 6 years among adult survivors of nonpituitary brain tumors with radiation exposure,[7] and 82[8] to 93%[9] for long-term survivors (greater than 10 years) of nasopharyngeal carcinoma. There is a well-characterized dose-dependent sequence of pituitary derangements, with the somatotrophs more likely to be affected first at even low radiation doses; gonadal, adrenal, and thyroid axes are more likely to become dysfunctional with higher radiation doses and with increased time out from radiation.[4,10] A more recent publication[11] found a dose threshold for endocrine dysfunction at 30 Gy in their skull base tumor case–control study, finding that thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone deficiencies are rare in those receiving less than 50 Gy.

As cancer treatment paradigms have changed for certain sinonasal malignancies, with an increase in chemoselective and chemoradiation protocols, it is imperative to continue to measure and evaluate quality of life (QoL), as well as potential known side effects of treatment. QoL is a multidimensional concept consisting of many different factors, including mental, social, and emotional well-being, financial burden, pain control, physical functioning, and cosmesis.[12] There are a variety of different QoL assessment tools. These tools can assess QoL generally or be disease-specific, allowing a more targeted analysis of specific aspects pertaining to that disease. The Anterior Skull Base Questionnaire (ASBQ), developed and validated by Gil et al,[13,14] is a patient-reported, disease-specific QoL survey for benign and malignant pathologies.

Radiotherapy has been shown to be an independent negative prognostic factor for QoL among head and neck cancer patients using multiple disease-specific QoL assessment tools,[2,15] including the ASBQ (specifically in the physical symptoms and impact on emotions domains).[13,14,16] Löfdahl et al[2] demonstrated this decreased QoL even in patients without hypopituitarism compared with healthy controls without radiation, most likely due to nonendocrine side effects of radiation. Other factors that have been shown to decrease QoL among skull base surgical patients in at least one domain of the ASBQ are malignancy, older age, female gender, repeat surgeries, wider resections, nasoseptal flap reconstruction, and classic surgical approach (compared with combined subcranial approach),[12–14,16,17] although these covariates may not be predictive for those patients whose surgeries were done endoscopically.[12,16,18,19]

Hypopituitarism has been associated with decreased QoL, especially if the patient is also suffering from depression, has negative illness perceptions, and/or lives in a rural community.[20] Conversations around QoL specifically among patients with RIH have focused on the deleterious effects of growth hormone deficiency (GHD), and how QoL can be improved with growth hormone replacement.[20,21] It has more recently been speculated that this decrease in QoL from GHD is more related to supraphysiological treatment with hydrocortisone at doses above 20 mg per day rather than GHD itself.[15] There have been few studies on the effect of RIH beyond GHD apart from those with pituitary adenomas and craniopharyngiomas.[20,22] To our knowledge, there have not been any investigations into QoL of radiated sinonasal cancer survivors who develop hypopituitarism compared directly to those who do not develop hypopituitarism. Furthermore, there have been no formal studies into the effect of hormonal replacement, outside of growth hormone replacement, on QoL. Untreated central adrenal insufficiency, hypothyroidism, and hypogonadism can cause severe fatigue, sexual dysfunction, negative body image perception, and reduced bone density,[6] among other symptoms, all of which can lead to decreased QoL, in surplus of the already decreased baseline QoL in those with skull base radiation. Given this known clinical sequalae, this study aimed to formally evaluate QoL among RIH patients compared with non-hypopituitary patients and the effect of treatment.

Materials and Methods

Data collection: A retrospective review of patients prospectively enrolled in an Institutional Review Board (IRB)-approved anterior skull base registry (IRB HUM003673) at a tertiary care center between the years 2011 and 2020 was performed. The anterior skull base registry is hosted on our institution's REDCap[23] platform. Included patients were those with a history of anterior skull base tumor, underwent at least one round of radiation to the primary site in the skull base, and had filled out at least one ASBQ at some point after their radiation treatment. Radiation therapy could include either intensity-modulated radiation therapy (IMRT), photon therapy, or stereotactic radiosurgery (e.g., SRS or gamma knife). Subjects with pituitary adenomas and without pituitary serologies, unless they had a known diagnosis in their chart relating to their pituitary function, were excluded. A total of 145 patients met inclusion and exclusion criteria. Comprehensive retrospective data was extracted from the patient chart using manual review and DataDirect software,[24] including tumor type, date of initial radiation, dates of subsequent biochemical and clinical follow-up, age, gender, type of skull base radiation, radiation dose, history of

systemic antitumor therapies (chemotherapy, immunologics, or hormonal therapies), length of follow-up, and death.

Evaluation of QoL: Our primary outcome was the ASBQ score. The ASBQ contains 35 questions, each on a 5-point Likert scale, with an option of choosing 1, 2, 3, 4, or 5. Note that 1 indicates poor QoL, whereas 5 indicates excellent QoL. Total scores thus range from 35 to 175. There are multiple domains within the ASBQ including performance, physical function, vitality, body pain, impact on emotions, and specific skull base symptoms. Although only 145 patients were included in this study, most of the subjects had filled out multiple ASBQ surveys at various time points after radiation, for a total of 330 surveys analyzed. For the purposes of this study comparing postradiation scores, preradiation surveys were not analyzed. For each survey the patient took, we assigned a "pituitary function status," which could be one of four levels: (1) never-hypopit, (2) pre-hypopit, (3) hypopit, and (4) treated hypopit. The never-hypopit status was assigned to subjects that did not have any evidence of pituitary dysfunction at the time of their survey and never went on to develop pituitary dysfunction at any point in their treatment course. Pre-hypopit status was assigned to a patient that did not have any evidence of pituitary dysfunction at the time of the survey but went on to develop hypopituitarism in the future. Pre-hypopit also included those subjects who ultimately developed hypopituitarism, but it was unclear at the time of that specific survey if they had yet developed any pituitary dysfunction based on serological tests (although clinically they had no pituitary symptomology). The third level, "hypopit," was assigned to subjects who demonstrated clear biochemical evidence of pituitary dysfunction at the time of their survey. "Treated hypopit" was assigned to subjects who were on some type of hormone replacement for their hypopituitarism (including hydrocortisone or other formulations of synthetic cortisol, testosterone injections or gel, estradiol therapy, or levothyroxine) at the time of their survey. Those who were on a hormone replacement therapy but still had serological evidence of hypopituitarism were assigned to the hypopit category. Patients often completed their ASBQ at the time of their pituitary screening laboratories, or during one of their cancer surveillance or endocrine follow-up visits. However, there were some asynchronous survey dates. In these cases, pituitary function status was assigned based on the most recent laboratory values.

Evaluation of endocrinopathy: As there has been increasing understanding of RIH over the past few decades, our institution has strived to achieve comprehensive pituitary screening profiles annually after completion of radiation. These screening serologies include 8 a.m. cortisol, prolactin, growth hormone (GH), insulin-like growth factor 1, free T4, TSH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and bioavailable testosterone. Although annual screening is our gold standard, some patients opted to receive their endocrine follow-up closer to home or were not able to come in to draw laboratories every year. In these cases, we used the laboratory values and clinical notes that were available to us, including those from accessible outside records.

If a patient had an abnormal serology, this often prompted a comprehensive evaluation in our Pituitary Endocrine Clinic. For these patients, the diagnosis given via clinical evaluation was used in our analysis. For those remaining few patients, available serologies were reviewed in detail. To be considered "hypopit" a subject must have demonstrated serologic evidence of at least one of the following: central hypogonadism, central hypothyroidism, and/or secondary adrenal insufficiency. Secondary/central hypogonadism was documented in premenopausal women by the finding of amenorrhea or oligomenorrhea in the setting of low LH and FSH concentrations, and in postmenopausal women with inappropriately low LH and FSH. In men, secondary hypogonadism was documented by finding low serum bioavailable testosterone in the setting of inappropriately nonelevated LH and FSH. Secondary hypothyroidism was defined as low free T4 concentration with nonelevated TSH. Secondary adrenal failure was defined by a morning cortisol less than 5 µg/dL.[25] At our institution, abnormal levels of GH are rarely treated as isolated clinical entities, and isolated GHD was not used in our hypopituitarism criteria.

Statistical analysis: Data were tabulated in an Excel spreadsheet (Excel 2007, Microsoft, Redmond, Washington, United States) and analyzed in SAS 9.3 (SAS Institute, Cary, North Carolina, United States). Pooled *t*-test and Wilcoxon signed rank test were used for bivariate analysis comparing continuous demographic variables by overall binary hypopituitarism status for parametric and nonparametric variables, respectively. Chi-squared tests and simple logistic regression were used for categorical variables. Ideally, we would compare each patient to themselves. However, because not everyone had ASBQ scores at all time points, with multiple surveys done per patient over time, we employed expert statistical consultation (E.B.) who suggested and performed three different statistical models with the primary outcome of ASBQ score. For each model, Likert scores were averaged per domain and overall. Model 1 tested group differences using a nonparametric Wilcoxon signed rank test with pairwise comparisons. This model takes all ASBQ scores as unique snapshots in time. Model 2 used a linear mixed effects model to account for intraperson correlation with a random intercept and random slope included for time since radiation. Model 3 was an adjusted linear mixed effects model that, in addition to accounting for intraperson correlation, adjusted for years out from radiation, age, sex, tumor pathology, radiation dose, type of radiation, and history of systemic antitumor therapy (including chemotherapy). Model 3 is particularly useful given our data set's lack of robust paired data (surveys done at the pre-hypopit vs. hypopit time points for the same person) by adjusting for variables that vary from person-to-person and likely have an impact on QoL. Statistical significance level was set to $\alpha < 0.05$.

The minimal clinically important difference (MCID) was calculated using methodology by Norman et al[26] of half of the standard deviation of sample in question.

Results

►**Table 1** demonstrates the demographic characteristics of our sample population. Overall, 145 patients were included in this study, with 35.2% ($n = 51$) of them developing hypopituitarism at some point in their treatment course. This aligns with our previously published institutional cohort hypopituitarism rate of 37%.[5] There were no significant differences between the non-hypopituitarism and hypopituitarism groups except for in length of follow-up and overall incidence of death as of the time of final analysis (January 2022). ►**Table 2** shows the types of tumor pathologies included, with the most patients having either squamous cell carcinoma or esthesioneuroblastoma. The vast majority of patients had malignant tumors, although we did include six with meningiomas and eight with craniopharyngiomas.

►**Table 3** summarizes the results of our three statistical models looking at the primary outcome of average ASBQ score per domain and overall. In model 1, each of the categories of the pituitary function status was compared with each other. Models 2 and 3 compared the never-hypopit to the three other groups (pre-hypopit, hypopit, and treated hypopit). Never-hypopit was chosen over pre-hypopit as the reference group due to a much higher total number of surveys in the never-hypopit category, and there were no statistical differences between the never-hypopit and pre-hypopit groups. Across all models, there was a statistically significant difference in overall QoL scores between never-hypopit and hypopit. Those with hypopituitarism at the time of the survey had overall average QoL scores ranging from 0.24 to 0.45 points (on a 5-point Likert scale) lower than those without hypopituitarism at the time of the survey (model 1 p 0.0004 compared with never-hypopit; p 0.049 compared with pre-hypopit). Model 1 surpassed the MCID. ►**Fig. 1** shows the changes in overall mean QoL across the four pituitary function status groups using model 1. The hypopit group had significantly lower scores than the non-hypopit group in at least two of three models across every ASBQ domain except for impact on emotions and physical functioning.

In regard to treatment, the treated (i.e., hormone-replaced) patients in general had higher QoL than the hypopit group (►**Fig. 2**); however, this increase did not reach statistical significance, but did surpass the MCID in the vitality domain. When comparing the treated group to the never-hypopit controls, treated patients had overall lower scores which reached statistical significance mostly in model 3 in the specific symptoms and pain domains, as well as overall (although only reaching a clinically detectable difference in the pain domain), reflecting that treatment may not fully restore baseline postradiation levels of QoL looking at aggregate data. However, this treatment effect seems to be modulated by the amount of time that has passed since radiation. We divided the ASBQ surveys into the following three subcategories, 0 to 2, 2 to 5, and 5+ years out from radiation, to better assess this longitudinal effect of QoL over time. Using

Table 1 Demographic characteristics, stratified by overall binary pituitary function status

Mean (SD) Percent (count)	All ($n = 145$)	Non-hypopit ($n = 94$)	Hypopit ($n = 51$)	p-Value
Age at time of radiation (y)	52.2 (14.8)	53.0 (15.5)	50.6 (13.3)	0.3624[a]
Sex				
Male	59.3% (86)	56.4% (53)	64.7% (33)	0.3300[b]
Female	40.7% (59)	43.6% (41)	35.3% (18)	
Type of skull base radiation				0.7643[b]
IMRT	89.7% (130)	88.3% (83)	92.2% (47)	ref
Proton	7.59% (11)	8.51% (8)	5.88% (3)	0.8692[d]
Gamma/stereotactic	2.76% (4)	3.19% (3)	1.96% (1)	0.7886[d]
Skull base total radiation dose	71.4 (27.6) $n = 128$	73.0 (29.6) $n = 83$	68.3 (23.5) $n = 45$	0.1997[c]
Antitumor therapy				0.3467[b]
Nothing	44.8% (65)	42.6% (40)	49.0% (25)	Ref
Chemotherapy	49.7% (72)	50.0% (47)	49.0% (25)	0.3388[d]
Other (immunologic, hormonal)	5.52% (8)	7.45% (7)	1.96% (1)	0.1980[d]
Length of follow-up (y)	6.47 (5.29)	5.76 (4.99)	7.78 (5.61)	0.0098[c]
Death	25.5% (37)	34.0% (32)	9.8% (5)	0.0014[b]

Abbreviations: IMRT, intensity-modulated radiation therapy; SD, standard deviation.
[a]Pooled t-test.
[b]Chi-squared test.
[c]Wilcoxon rank-sum test.
[d]Simple logistic regression.

Table 2 Types of tumor pathologies included ordered by decreasing sample incidence

Count	All ($n = 145$)	Non-hypopit ($n = 94$)	Hypopit ($n = 51$)
Squamous cell carcinoma	32	26	6
Esthesioneuroblastoma	30	19	11
Sinonasal undifferentiated	11	5	6
Chordoma	10	8	2
Other sarcoma	10	7	3
Melanoma	8	7	1
Craniopharyngioma	8	0	8
Neuroendocrine	7	3	4
Adenocarcinoma	7	4	3
Meningioma	6	5	1
Adenoid cystic carcinoma	6	5	1
Metastasis	3	2	1
Chondrosarcoma	3	1	2
Nasopharyngeal	1	0	1
Plasmacytoma	1	1	0
Lymphoepithelioma	1	1	0
Acinic cell carcinoma	1	0	1

model 1, comparing to the hypopit group, treatment seemed to improve QoL scores, at least clinically in the 0- to 2-year range out from radiation (estimated 0.22 point average increase, p 0.876), decrease scores in the 2- to 5-year range (estimated 0.32 point average decrease, p 0.572), and significantly increase scores in the 5+ year range out from radiation (estimated 0.42 point average increase, p 0.041) (►**Tables 4** and **5**). ►**Fig. 3** shows the boxplots comparing the QoL scores between the pituitary function statuses across these three time-based subgroups.

Overall, the never-hypopit and pre-hypopit groups had similar QoL. The fully adjusted model 3 revealed a difference in QoL between tumor pathologies across all domains, with plasmacytoma and adenocarcinoma having consistently worse QoL scores across most domains. On average, adenocarcinoma patients had a mean QoL score 0.685 points lower than squamous cell carcinoma patients (p 0.0045); plasmacytoma patients had an estimated mean QoL score 0.910 points lower than squamous cell carcinoma patients ($p < 0.0001$) holding all other variables constant. Interestingly, older age at the time of radiation was a protective factor only in the impact on emotions domain, with an increase of 0.01 points for every additional year of age (p 0.0012) holding all other variables in the model constant. There were no significant differences in QoL between males and females except in the impact on emotions domain, where females on average score 0.19 points lower (p 0.0288).

Discussion

These data confirm our hypothesis that patients with RIH beyond GHD have significantly lower QoL compared with those who do not develop hypopituitarism after radiation. This was true across most domains (except impact on emotions) and statistical models, even among those with the same age, sex, time out from radiation, type of tumor, type of radiation, and radiation dose (model 3). Our average ASBQ QoL score, no matter the hypopituitarism status, was relatively high, at 3.13, corresponding to "good" QoL, but this decreased to a greater degree than the MCID (greater than a 7.9% decrease) when going from non-hypopit to hypopit, at least in model 1. The largest average drop in scores comparing non-hypopit to hypopit was in the body pain domain (–0.72), which correlates to an 18% decrease in QoL. Though not dramatic, it does surpass the MCID, meaning patients are able to perceive a difference in their QoL. Model 3 showed a statistically significant decrease in overall QoL, although it did not surpass the MCID except for in the physical function, vitality, and body pain domains. This suggests that hypopituitarism most affects functioning, vitality, and pain after controlling for other variables that could be contributing to QoL. This aligns with the symptom profile of overwhelming fatigue and subsequent lack of daily life functioning often seen in patients with central hypothyroidism or secondary adrenal insufficiency. The specific symptoms domain, which asks about specific symptoms related to skull base patients (changes in vision, appetite, taste, smell, appearance, and secretions), had the lowest average scores (2.70). Factors such as age and gender seemed to impact the emotions domain more than pituitary function status among these radiated patients, perhaps due to the development of beneficial coping mechanisms to chronic illness as patients age.

As for the differences in the demographics between the hypopituitarism and non-hypopituitarism groups, those in the hypopituitarism group were followed on average for 7.78 years, compared with 5.76 years for those in the non-hypopituitarism group (p 0.0098). This can most likely be attributed to the potential higher motivation among hypopituitarism patients to maintain endocrine follow-up given their symptoms and need for treatment, particularly opting for follow-up at our institution's pituitary clinic, making their records more easily accessible. This length of follow-up discrepancy could also be explained by the higher rate of death in the non-hypopituitarism group (34%) compared with the hypopituitarism group (9.8%) (p 0.0014). This seemingly contradicts the previous finding that hypopituitarism is associated with a 55% increase in mortality, particularly in nonreplaced patients with history of radiation.[27] However, in our cohort, we hypothesize that patients in the non-hypopituitarism group were not living long enough to develop or be diagnosed with hypopituitarism. There is a concern that this shorter follow-up time and higher incidence of death in the non-hypopituitarism group could be artificially enhancing for more aggressive tumors, and thus death occurred before hypopituitarism status was fully realized. However, if this was the case, we still found that the

Table 3 Pairwise comparisons of ASBQ QoL scores between pituitary function status groups by ASBQ domains, comparing statistical models 1 to 3

Model 1: Actual difference (*p*-value) Model 2 and 3: Estimated difference (*p*-value)	Never-hypopit versus pre-hypopit	Never-hypopit versus hypopit	Never-hypopit versus treated hypopit	Pre-hypopit versus hypopit	Hypopit versus treated hypopit
Performance					
Model 1	−0.168 (0.368)	−0.325 (0.012)[ab]	−0.202 (0.215)	−0.157 (0.721)	0.123 (0.883)
Model 2	−0.138 (0.139)	−0.230 (0.023)[a]	−0.132 (0.256)		
Model 3	−0.195 (0.062)	−0.293 (0.009)[a]	−0.209 (0.100)		
Physical function					
Model 1	0.002 (0.994)	−0.610 (0.002)[ab]	−0.323 (0.117)[b]	−0.612 (0.028)[ab]	0.280 (0.727)
Model 2	−0.059 (0.730)	−0.277 (0.096)	−0.183 (0.282)		
Model 3	−0.136 (0.463)	−0.332 (0.064)[b]	−0.245 (0.184)		
Vitality					
Model 1	−0.165 (0.685)	−0.634 (< 0.0001)[ab]	−0.312 (0.096)[b]	−0.469 (0.052)[b]	0.322 (0.388)[b]
Model 2	−0.166 (0.216)	−0.385 (0.006)[ab]	−0.255 (0.080)		
Model 3	−0.174 (0.281)	−0.357 (0.012)[ab]	−0.270 (0.083)		
Body pain					
Model 1	−0.342 (0.372)[b]	−0.724 (0.003)[ab]	−0.482 (0.126)[b]	−0.381 (0.561)[b]	0.242 (0.767)
Model 2	−0.175 (0.409)	−0.447 (0.041)[ab]	−0.388 (0.103)[b]		
Model 3	−0.413 (0.065)[b]	−0.700 (0.003)[ab]	−0.655 (0.010)[ab]		
Impact on emotions					
Model 1	−0.085 (0.768)	−0.151 (0.564)	−0.002 (0.979)	−0.066 (0.996)	0.149 (0.888)
Model 2	−0.053 (0.644)	−0.104 (0.332)	−0.071 (0.467)		
Model 3	−0.098 (0.439)	−0.164 (0.175)	−0.100 (0.368)		
Specific symptoms					
Model 1	−0.041 (0.999)	−0.331 (0.021)[ab]	−0.256 (0.174)	−0.290 (0.115)	0.075 (0.683)
Model 2	−0.012 (0.921)	−0.201 (0.064)	−0.203 (0.037)[a]		
Model 3	−0.077 (0.539)	−0.227 (0.041)[a]	−0.256 (0.016)[a]		
Overall QoL					
Model 1	−0.110 (0.882)	−0.454 (0.0004)[ab]	−0.253 (0.078)	−0.344 (0.049)[ab]	0.200 (0.663)
Model 2	−0.089 (0.377)	−0.240 (0.018)[a]	−0.177 (0.095)		
Model 3	−0.154 (0.182)	−0.278 (0.012)[a]	−0.236 (0.046)[a]		
MCID	0.297	0.314	0.300	0.317	0.308

Abbreviations: ASBQ, Anterior Skull Base Questionnaire; MCID, minimal clinically important difference; QoL, quality of life.
Note: Negative differential values indicate worsening QoL.
[a]*p*-Value < 0.05.
[b]Clinically significant.

non-hypopituitarism patients, even if they had more aggressive tumors, still had higher QoL than the hypopituitarism group, which further supports that hypopituitarism itself can predict lower QoL.

We found that the dose of skull base radiation (maximum dose to the primary tumor) did not significantly differ between the non-hypopituitarism and hypopituitarism groups (p 0.20). This seemingly contradicts the long-standing existing literature[5,6,28–31] that suggests a positive dose–responsive relationship between radiation dose and incidence of hypopituitarism, especially in the three axes we analyze in this study, although the data are mixed.[29] However, almost all of our patients received relatively high doses of radiation (average 71.4 Gy) due to the aggressive nature of these tumors, which is well above the thresholds discussed for developing hypopituitarism. Therefore, dose could be playing less of a role at these high radiation levels, and instead there are other factors contributing. Alternatively,

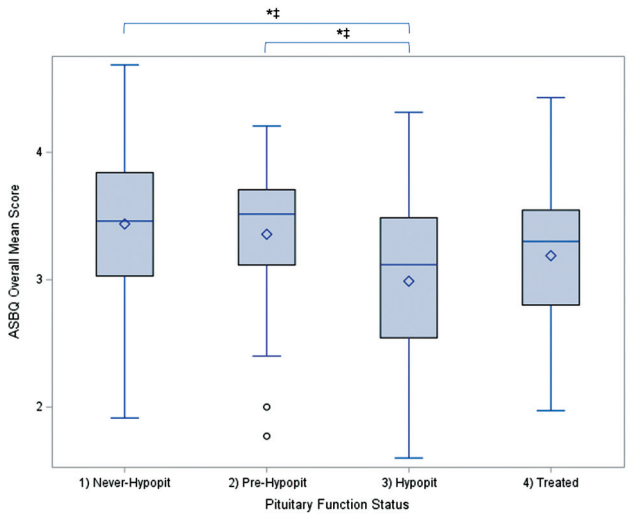

Fig. 1 ASBQ mean total score by pituitary function status using model 1. *p-value < 0.05, ‡clinically significant. ASBQ, Anterior Skull Base Questionnaire.

our sample size could potentially not be large enough to reach significance. Type of skull base radiation (IMRT vs. photon vs. stereotactic) did not seem to affect hypopituitarism status. Although there is a theoretical advantage to stereotactic and proton radiation compared with conventional radiotherapy, studies have not suggested a long-term difference in hypopituitarism between these groups in certain populations.[29,30,32–34] It is hypothesized that development of hypopituitarism after stereotactic radiation may be more dependent on tumor volume rather than radiation dosage.[35] Also, the vast majority (130, 90%) of patients underwent IMRT in this study, with only 15 who underwent either proton or stereotactic radiation therapy.

Treatment improved patients' QoL across all domains, though only surpassing the clinically noticeable difference in the vitality domain when analyzing all time points. Treatment often improves energy levels and thus the perception of vitality. However, these improvements in QoL did not reach a statistically significant level unless looking only at those patients greater than 5 years out from radiation. We hypothesize that these patients who were farther out from their radiation were not being recognized early for having hypopituitarism, and thus were not treated early on. They felt the full symptomatic burden of hypopituitarism without replacement (as evidenced by the large differential scores between never-hypopit and hypopit among these long-term survivors), and thus felt much better once treated. Whereas those who were recognized earlier were able to be treated quickly before dramatic symptoms developed. We hypothesize that those in the 2- to 5-year range may have experienced worsening QoL after treatment due to side effects of medications outweighing the perceived benefits of more subclinical hypopituitarism, although more research needs to be done to investigate this theory. This highlights the importance of repeated and consistent serological testing in

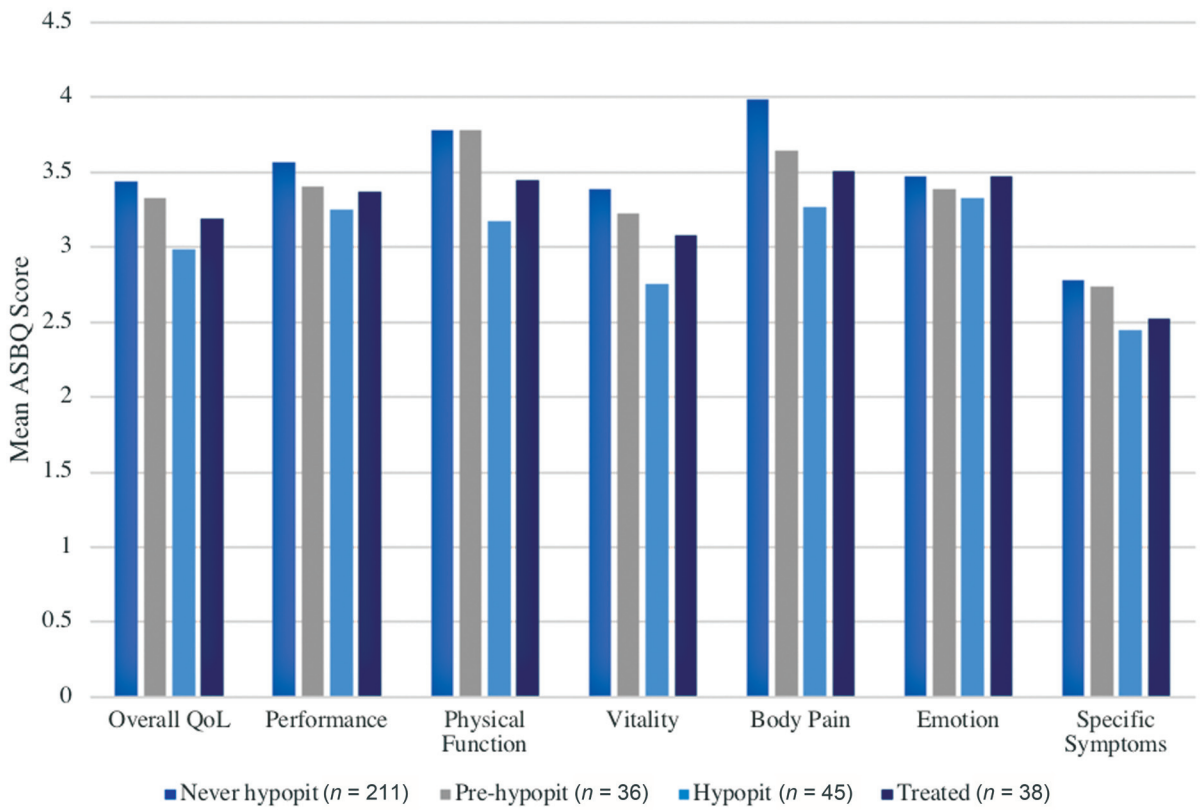

Fig. 2 Comparing mean ASBQ QoL scores per domain across the pituitary function status groups using model 1. ASBQ, Anterior Skull Base Questionnaire; QoL, quality of life.

Table 4 Averaged total ASBQ QoL scores per pituitary function status aggregated by years out from radiation groups (0–2 years, 2–5 years, and 5+ years)

Years out from radiation	Pituitary function status	*N*	Mean	Standard deviation	Minimum	Maximum
0–2 y	Never-hypopit	88	3.38746	0.6109	1.91429	4.68571
	Pre-hypopit	24	3.32393	0.44015	2.45714	4.02857
	Hypopit	15	3.08825	0.42199	2.54286	3.82857
	Treated	4	3.30714	0.3471	3	3.74286
2–5 y	Never-hypopit	76	3.43118	0.58777	2	4.62857
	Pre-hypopit	10	3.29353	0.89032	1.77143	4.20588
	Hypopit	14	3.19659	0.45146	2.37143	3.77143
	Treated	23	2.97107	0.50629	1.97143	3.65714
5+ y	Never-hypopit	47	3.55913	0.58295	2.23529	4.6
	Pre-hypopit	2	3.60882	0.01248	3.6	3.61765
	Hypopit	16	2.71098	0.85008	1.6	4.31429
	Treated	11	3.59901	0.57522	2.57143	4.42857

Abbreviations: ASBQ, Anterior Skull Base Questionnaire; QoL, quality of life.

these skull base radiation patients so that replacement can occur if needed at appropriate doses. Though the patient may not perceive an immediate improvement in QoL with hormonal replacement early on, early detection and appropriate replacement serves to prevent the significant potential decline in QoL if you wait greater than 5 years out from radiation (a 22% average drop). Those greater than 5 years out from radiation, when treated, on average were able to regain their QoL to at or above their non-hypopituitarism baseline after radiation. Currently, there is great variability in the follow-up of skull base malignancy patients after radiation, including timing and frequency of screening serologies and imaging. The National Comprehensive Cancer Network guidelines do not include comprehensive pituitary serologies in their follow-up recommendations for head and neck cancers after radiation except for TSH every 6 to 12 months after radiation.[36] This screening with serum TSH alone could mislead the clinician to believe the patient is euthyroid rather than central hypothyroid and thus in need of replacement. Similar confusion comes from the possible misinterpretation of gonadal dysfunction. Many of these patients also receive chemotherapy, which is known to reduce gonadal function, and therefore can hide a secondary diagnosis of radiation-induced hypogonadism.[37] Ideally, we need specific guidelines for pituitary screening serologies on irradiated sinonasal malignancies and skull base tumors.

There are certain limitations to our study. First, we had a lack of data. Although we aimed to have an annual comprehensive pituitary serology and ASBQ survey on each patient, this was not always possible. The realities of the coronavirus disease 2019 pandemic limited patient interactions, including laboratory draws and survey administration. Some patients would elect to get their hypopituitarism follow-up from an endocrinologist or primary care physician closer to home and would only come to our institution for cancer surveillance. Therefore, it was sometimes unclear what their pituitary function status was on the exact date of their ASBQ, or whether they had confirmatory gold standard testing for specific pituitary deficiencies. We tried to mitigate this by looking at outside records. In addition, model 3 analyzed a

Table 5 Actual differences in averaged total ASBQ QoL scores and *p*-values for two-sided multiple pairwise comparisons between the pituitary function status groups aggregated by years out from radiation

Actual difference (*p*-value[c])	0–2 years out from radiation	2–5 years out from radiation	5+ years out from radiation
Never-hypopit versus pre-hypopit	−0.0635 (0.9428)	−0.138 (0.9994)	0.050 (0.9993)
Never hypopit versus hypopit	−0.299 (0.1858)[b]	−0.235 (0.4940)	−0.848 (0.0045)[ab]
Never hypopit versus treated hypopit	−0.080 (0.9765)	−0.460 (0.0101)[ab]	0.040 (0.9999)
Pre-hypopit versus hypopit	−0.236 (0.3852)[b]	−0.097 (0.6811)	−0.898 (0.4962)[b]
Hypopit versus treated hypopit	0.219 (0.8764)[b]	−0.322 (0.5729)[b]	0.888 (0.0412)[ab]

Abbreviations: ASBQ, Anterior Skull Base Questionnaire; QoL, quality of life.
[a]*p*-Value < 0.05.
[b]Clinically significant.
[c]Wilcoxon signed rank test.

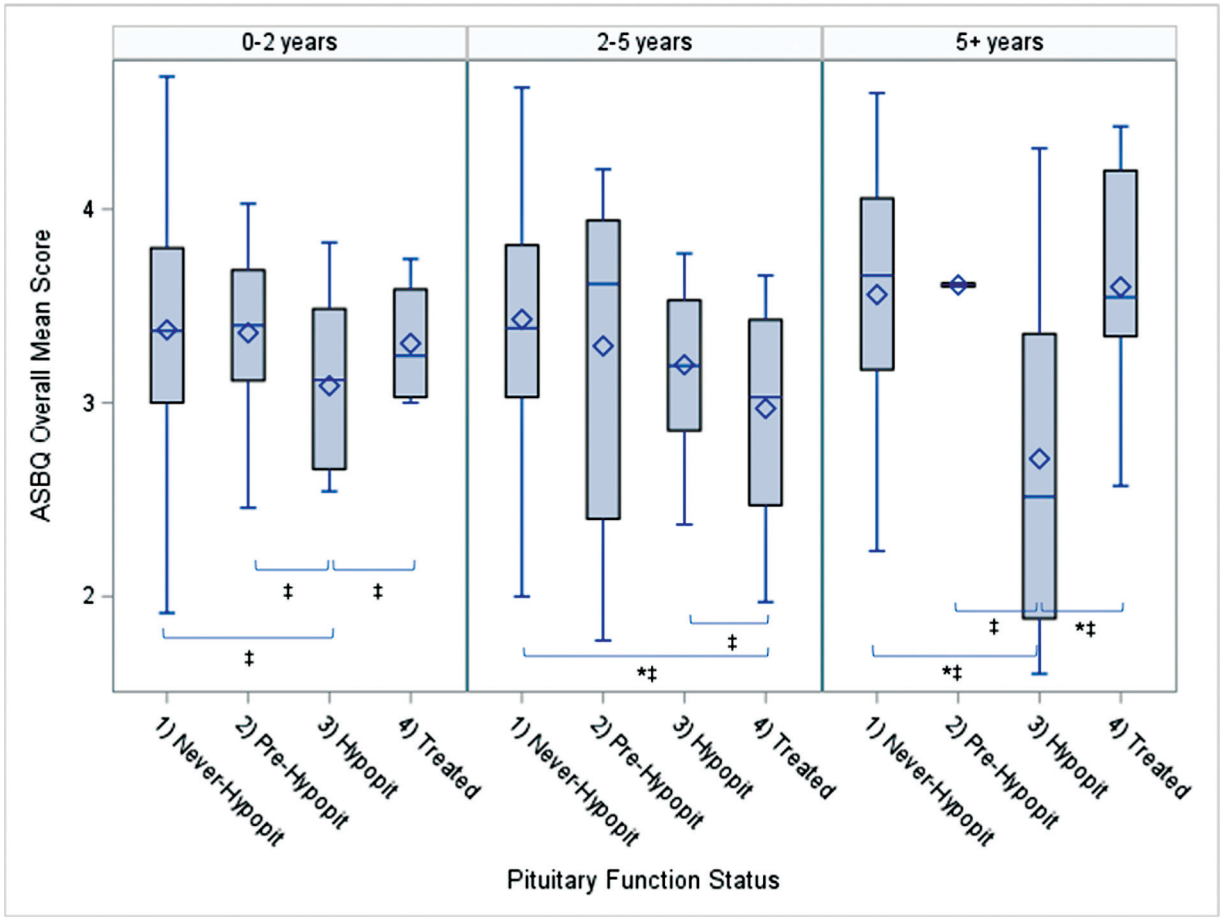

Fig. 3 Comparisons of mean ASBQ QoL scores between pituitary function status groups across years out from radiation using model 1. *p-value < 0.05, ‡clinically significant. ASBQ, Anterior Skull Base Questionnaire; QoL, quality of life.

reduced number of surveys (ranging from $n = 294$–299) due to lack of certain demographic or clinical data that were adjusted for in the model. Second, given the inconsistency of ASBQ administration, we did not require patients to have a baseline ASBQ before radiation, since the effect of radiation on QoL was not within the scope of our study, and we did not feel it would be scientifically sound to ask patients to retrospectively recall their QoL. We also did not require, again due to lack of data, every hypopituitarism patient to have both a pre- and post-hypopituitarism ASBQ to directly compare. Only 16 patients in our data set had at least one survey taken after radiation when they were pre-hypopit and again when hypopit. Among these patients, a paired Wilcoxon signed rank test with continuity correction showed no significant overall difference between pre-hypopit and hypopit with an estimated difference of 0.084 (95% confidence interval = –0.113, 0.177, p 0.229). However, this interpretation using paired data are limited given the low number of patients precluding a robust statistical analysis. Alternatively, we were able to include more patients by extrapolating data from the entire sample population through statistical models (namely models 2 and 3) that accounted for person-to person variability in QoL via intra-person correlation between the multiple ASBQ surveys that each individual did have, even if they did not have surveys specifically at the pre-/post-hypopituitarism or pre-/post-treatment time points. Furthermore, model 3 attempted to adjust for person-to-person variability of key demographic and tumor-specific variables finding that QoL scores among those with the same age, sex, years out from radiation, tumor pathology, radiation type, radiation dose, and chemotherapy status but had hypopit were lower than the QoL among those without hypopituitarism. Third, almost all patients in the anterior skull base registry had one or multiple surgeries before radiation, so there is a possibility that their hypopituitarism could have been due to direct surgical damage as opposed to radiation-induced damage. Regardless of etiology, the trend still holds for decreased QoL among hypopituitary patients after radiation compared with non-hypopituitary patients after radiation. Hypopituitarism seems to most impact the vitality and body pain domains across all models to a clinical and statistically significant degree. We acknowledge the need for more studies that can prospectively and comprehensively collect a longitudinal data set to examine intra-person correlation directly or be able to better match non-hypopituitary controls to hypopituitary cases. Although a preliminary study, the advantages were that this was a longitudinal study over the course of 9 years with multiple data points per individual. We had a relatively large sample size given the rarity of these tumors.

Conclusion

This is the first study to formally confirm the hypothesis that RIH causes decreased QoL among skull base and sinonasal tumor patients. The data supports that awareness, early detection of hypopituitarism via consistent and comprehensive pituitary serologies, and appropriate medical treatment and psychosocial interventions can prevent longer term detrimental impact on QoL.

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Conflict of Interest
None declared.

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References

1 Lam KS, Tse VK, Wang C, Yeung RT, Ho JH. Effects of cranial irradiation on hypothalamic-pituitary function–a 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med 1991;78(286):165–176
2 Löfdahl E, Berg G, Johansson KA, et al. Compromised quality of life in adult patients who have received a radiation dose towards the basal part of the brain. A case-control study in long-term survivors from cancer in the head and neck region. Radiat Oncol 2012; 7:179
3 Fernandez A, Brada M, Zabuliene L, Karavitaki N, Wass JA. Radiation-induced hypopituitarism. Endocr Relat Cancer 2009;16(03): 733–772
4 Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. Pituitary 2009;12(01):40–50
5 VanKoevering KK, Sabetsarvestani K, Sullivan SE, Barkan A, Mierzwa M, McKean EL. Pituitary dysfunction after radiation for anterior skull base malignancies: incidence and screening. J Neurol Surg B Skull Base 2020;81(01):75–81
6 Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. Nat Clin Pract Endocrinol Metab 2009;5(02):88–99
7 Agha A, Sherlock M, Brennan S, et al. Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab 2005;90(12):6355–6360
8 Ratnasingam J, Karim N, Paramasivam SS, et al. Hypothalamic pituitary dysfunction amongst nasopharyngeal cancer survivors. Pituitary 2015;18(04):448–455
9 Ipekci SH, Cakir M, Kiyici A, Koc O, Artac M. Radiotherapy-induced hypopituitarism in nasopharyngeal carcinoma: the tip of an iceberg. Exp Clin Endocrinol Diabetes 2015;123(07):411–418
10 Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993;328(02):87–94
11 Vakilian S, Thébaut J, Ruo R, et al. Examination of the dose-effect relationship of radiation-induced hypopituitarism: results of a case-control study. Adv Radiat Oncol 2021;6(04):100693
12 Kirkman MA, Borg A, Al-Mousa A, Haliasos N, Choi D. Quality-of-life after anterior skull base surgery: a systematic review. J Neurol Surg B Skull Base 2014;75(02):73–89
13 Gil Z, Abergel A, Spektor S, Shabtai E, Khafif A, Fliss DM. Development of a cancer-specific anterior skull base quality-of-life questionnaire. J Neurosurg 2004;100(05):813–819
14 Gil Z, Abergel A, Spektor S, et al. Quality of life following surgery for anterior skull base tumors. Arch Otolaryngol Head Neck Surg 2003;129(12):1303–1309
15 Ajmal A, McKean E, Sullivan S, Barkan A. Decreased quality of life (QoL) in hypopituitary patients: involvement of glucocorticoid replacement and radiation therapy. Pituitary 2018;21(06): 624–630
16 Abergel A, Cavel O, Margalit N, Fliss DM, Gil Z. Comparison of quality of life after transnasal endoscopic vs open skull base tumor resection. Arch Otolaryngol Head Neck Surg 2012;138(02): 142–147
17 Fliss DM, Abergel A, Cavel O, Margalit N, Gil Z. Combined subcranial approaches for excision of complex anterior skull base tumors. Arch Otolaryngol Head Neck Surg 2007;133(09):888–896
18 McCoul ED, Anand VK, Schwartz TH. Improvements in site-specific quality of life 6 months after endoscopic anterior skull base surgery: a prospective study. J Neurosurg 2012;117(03): 498–506
19 McCoul ED, Anand VK, Bedrosian JC, Schwartz TH. Endoscopic skull base surgery and its impact on sinonasal-related quality of life. Int Forum Allergy Rhinol 2012;2(02):174–181
20 Crespo I, Santos A, Webb SM. Quality of life in patients with hypopituitarism. Curr Opin Endocrinol Diabetes Obes 2015;22 (04):306–312
21 Rosén T, Wirén L, Wilhelmsen L, Wiklund I, Bengtsson BA. Decreased psychological well-being in adult patients with growth hormone deficiency. Clin Endocrinol (Oxf) 1994;40 (01):111–116
22 Erfurth EM, Holmer H, Fjalldal SB. Mortality and morbidity in adult craniopharyngioma. Pituitary 2013;16(01):46–55
23 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(02): 377–381
24 Kheterpal S. Data Direct: a self-serve tool for data retrieval. University of Michigan Medical School Office of Research 2022. Available at: https://research.medicine.umich.edu/sites/default/files/doctr_datadirect_user_guide_2019-10-03.pdf, 22 Nov 2016
25 Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. J Clin Endocrinol Metab 1998;83(07):2350–2354
26 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41(05):582–592
27 Jasim S, Alahdab F, Ahmed AT, et al. Mortality in adults with hypopituitarism: a systematic review and meta-analysis. Endocrine 2017;56(01):33–42
28 Castinetti F. Radiation techniques in aggressive pituitary tumours and carcinomas. Rev Endocr Metab Disord 2020;21(02):287–292
29 Sathyapalan T, Dixit S. Radiotherapy-induced hypopituitarism: a review. Expert Rev Anticancer Ther 2012;12(05):669–683
30 Darzy KH. Radiation-induced hypopituitarism. Curr Opin Endocrinol Diabetes Obes 2013;20(04):342–353
31 Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. Q J Med 1989;70(262): 145–160
32 Minniti G, Gilbert DC, Brada M. Modern techniques for pituitary radiotherapy. Rev Endocr Metab Disord 2009;10(02): 135–144
33 Höybye C, Grenbäck E, Rähn T, Degerblad M, Thorén M, Hulting AL. Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic

radiosurgery. Neurosurgery 2001;49(02):284–291, discussion 291–292
34 Chan LF, Storr HL, Plowman PN, et al. Long-term anterior pituitary function in patients with paediatric Cushing's disease treated with pituitary radiotherapy. Eur J Endocrinol 2007;156 (04):477–482
35 Mitsumori M, Shrieve DC, Alexander E III, et al. Initial clinical results of LINAC-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. Int J Radiat Oncol Biol Phys 1998;42(03):573–580
36 Pfister DG, Spencer S, Adelstein D, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020;18(07):873–898
37 Isaksson S, Bogefors K, Ståhl O, et al. High risk of hypogonadism in young male cancer survivors. Clin Endocrinol (Oxf) 2018;88(03): 432–441