Taste and Smell Functions in Long-term Survivors after Childhood Medulloblastoma/CNS-PNET

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Research Article

Keywords: Medulloblastoma, CNS-PNET, pediatric cancer survivors, long-term effects, taste, smell

Posted Date: January 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1160507/v1

Version of Record: A version of this preprint was published at Supportive Care in Cancer on April 15th, 2022. See the published version at https://doi.org/10.1007/s00520-022-07048-9.

Abstract

Purpose Our aim was to investigate taste and smell functions in survivors, with a minimum of 2 years follow-up time, after treatment of childhood medulloblastoma/CNS-PNET.

Methods This cross-sectional study included 40 survivors treated ≤ 20 years of age. Taste strips with four concentrations of sweet, sour, salt, and bitter were used to assess taste function in all participants. Score from 0-16; ≥ 9 normogeusia, < 9 hypogeusia, and complete ageusia which equals no sensation. No sensation of a specific taste quality equals ageusia of that quality. Thirty-two participants conducted smell testing using three subtests of Sniffin' sticks; threshold, discrimination, and identification. Together they yield a TDI-score from 1-48; functional anosmia ≤ 16.00, hyposmia >16.00 - < 30.75, normosmia ≥ 30.75 - < 41.50, and ≥ 41.50 super smeller. Results were compared with normative data. Survivors subjectively rated their taste and smell functions using a numerical rating scale (NRS) score 0-10.

Results Forty survivors with a mean follow-up of 20.5 years, 13 (32.5 %) were diagnosed with hypogeusia, nine (22.5 %) of these being ageusic of one or more taste qualities. Seventeen (53 %) of 32 participants were diagnosed with hyposmia. Comparing survivors with hyposmia to those with normosmia, a significant difference ($p<0.05$) was found in TDI-score and in all the subtests. The mean NRS score of subjective ratings of functions were high.

Conclusion Our study showed impaired taste and smell functions in long-term survivors of childhood MB/CNS-PNET using objective measurements. However, subjective ratings did not reflect objective findings.

Introduction

The embryonal tumors medulloblastoma (MB) and central nervous system supratentorial primitive neuroectodermal tumor (CNS-PNET) are malignant childhood brain tumors [1,2]. MB is located in the infratentorial brain and CNS-PNET in the supratentorial brain [1,2]. Both entities are treated similarly with a multidisciplinary approach involving surgery, radiotherapy (RT), and/or chemotherapy [2-4]. Due to the high risk of severe neurocognitive impairment, patients under the age of 3 to 5 years are treated without RT in most countries [4,5]. Although survival rates have improved [6], survivors of childhood MB/CNS-PNET may experience several complications and long-term effects such as posterior fossa syndrome, second primary neoplasm, hearing and visual impairment, cerebrovascular disease, and endocrinopathies [1,5,7,8].

Reduced or altered taste and smell functions are possible long-term effects of cancer treatment [9], and may have severe impact on patients' diet, nutritional status, and health maintenance [9,10], as well as quality of life [11]. Changes in taste and smell may be present before, during or after cancer treatment [9]. Most studies have investigated alterations during treatment [9,12,13], while less research has focused on taste and smell functions years after treatment [9]. Taste buds have a lifespan of approximately 10 days,

and are continuously replaced [14], while the olfactory neurons regenerate every 3 to 6 months [14]. Evidence regarding recovery of chemosensory functions in cancer survivors is conflicting [9].

Irreversible taste changes after RT in head-and neck cancer (HNC) patients are well known [10]. Taste impairment has been reported even when the irradiation field not directly involved the oral cavity [15]. Smell function may also be impaired in HNC patients [16, 17]. Only few studies have addressed taste and smell functions in survivors treated for other malignancies than HNC [18,19], and to our knowledge only a few have included CNS cancers like MB/CNS-PNET [18, 20, 21].

As most MB/CNS-PNET patients are treated with RT of the cranio-spinal axis [2-4] there is a risk of damage to healthy tissue in the head and neck region where smell and taste receptors are located [14, 22]. Johannesen and coworkers (2002) found taste impairment in three out of 33 brain tumor survivors treated with RT [20]. Leyrer and coworkers (2013) assessed taste and smell dysfunctions in patients after brain irradiation using a validated questionnaire [21]. They reported that 14 out of 20 patients experienced taste dysfunction, and 10 out of 20 smell impairment [21]. Including chemotherapy in the treatment of MB/CNS- PNET patients increases the risk for chemosensory damage [9, 23].

Due to limited studies on taste and smell functions in survivors of CNS cancers, especially in pediatric survivors, the aim of this study was to investigate objective, and subjective taste and smell functions in long-term survivors after childhood MB/CNS-PNET.

Material And Methods

Patients/study design

This cross-sectional study on taste and smell functions was part of a large regional multidisciplinary study investigating health impairments in survivors of pediatric MB/CNS-PNET [3, 24]. Participants had to 1) be treated at Oslo University Hospital (OUH) between January 1, 1974 and December 31, 2013, 2) have a histophatologically confirmed diagnosis of MB/CNS-PNET, 3) be diagnosed ≤ 20 years, and 4) have a minimum of 2 years observation time.

Participants underwent validated taste and smell functions tests (Burghart, Wendel, Germany), and a subjective evaluation of functions. Survivors aged <10 years at study start were excluded from participation [25] as were survivors unable to conduct tests due to severe cognitive and/or physical impairment after treatment. Information regarding each survivor's diagnosis, treatment and other relevant anamnestic information was gathered from the patient's medical charts.

All tests were performed by the same dentist in an examination room at OUH.

Subjective assessment of taste and smell

Survivors rated their subjective evaluation of taste and smell functions using a 0-10 numerical rating scale (NRS), with a lower number implying that they felt they had reduced sense after treatment of

MB/CNS-PNET. Participants not able to rate themselves due to severe neurocognitive impairment were excluded.

Test of smell function

Smell was assessed using the Sniffin' Sticks test from Burghart, Wendel, Germany. The test consists of three subtests; threshold test (THR), discrimination test (DIS), and identification test (ID). Together THR, DIS, and ID yield a score, the "TDI-score", which ranges between 1 and 48. Time spent administering all three tests was approximately 40 minutes. To minimize distractions the investigator used odourless gloves, and no perfumed body products.

Threshold test (THR)

THR is performed in a "staircase procedure", where the participant in each step is presented with three Sniffin' pens (triplets). In each triplet, there is two pens without odour and one with odour, n-Butanol. The kit consists of 16 triplets, where triplet number 1 contains the pen with the highest concentration of the odour, and triplet number 16 contain the pen with the lowest concentration. First, the participant is presented with the pen with the highest concentration, to be familiarized with the odour. The pen is held in front of the nostrils for a few seconds. Then the subject is exposed to the triplets from low to high concentration, and asked to recognize the pen in each triplet with the odour. If the answer is correct, pens in the same triplet are shuffled and presented again. If the correct answer is given again, the examiner does a reversal of the "staircase procedure" until the subject can´t recognize the pen with the odour in a triplet. The test is over when the participant has been presented with seven staircase reversal steps, and the final score is the mean value of the last four reversal steps.

Discrimination test (DIS)

The aim of this test is to investigate if a subject can differentiate smells. The participant is presented with 16 different triplets of Sniffin' pens. In each triplet, there is two pens with the same odour and one pen with a different odour. The task is to identify the one pen that smells different. The participant always has to provide an answer, "three-alternative forced choice". Each pen is presented below the nostrils once for a few seconds with approximately 5 seconds between each pen in a triplet, and approximately 30 seconds between each triplet. The score for DIS can range between 0 to 16.

Identification test (ID)

ID consists of 16 pens with different odours. The aim of this test is to assess if the participant is able to identify everyday odours. Each pen contains a familiar odour, and is held below the participant's nose for a few seconds one time. The participant is asked to identify the odour by choosing one of four alternatives for each pen, presented on a multiple-choice card. Even if the participant is not sure, he or she has to make a choice. The interval between each pen is approximately 30 seconds. Maximum score of the ID is 16.

Normative values for smell

Each participant's TDI-score, was compared with normative data and classification from Olesziewicz and coworkers (2019) [25], where a participant with a TDI-score of 1) ≤ 16.00 is regarded as having functional anosmia, 2) > 16.00 and < 30.75 is regarded as having hyposmia, 3) ≥ 30.75 and < 41.50 is regarded as having normosmia, and 4) ≥ 41.50 referred to as super smeller [25].

Test of taste function

Taste function was evaluated using taste strips (Burghart, Wedel, Germany), and the test took approximately 20 minutes for each participant. The test consists of filter-paper strips impregnated with four different concentrations of taste solutions of either sweet, salt, sour or bitter. The concentrations for each of the tastes are as following: sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose, sour: 0.3, 0.165, 0.09, 0.05 g/ml citric acid, salty: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride, and bitter: 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride [26, 27]. Strips with different taste qualities were randomly presented, one at a time from low to high concentration, to the anterior part of the tongue, and the participant were asked to identify the taste. Even if the participants did not sense a taste, they had to answer in a "forced-choice" procedure. The participant was asked to rinse their mouth with a sip of water between each strip. Total correct identification score was 16, with four correct scores for each taste quality. Evaluation of each participant's taste-score was based on normative values [27] as instructed in the test protocol: normogeusia ≥ 9, hypogeusia < 9, and no sensation = complete ageusia (Burghart protocol) [27]. The taste function for each taste quality was assessed as normogeusia when ≥2 correct identifications of sweet, sour and salty, and ≥1 for bitter, while no taste sensation was regarded as ageusia of that specific taste quality.

Statistical analysis

Descriptive statistics were used on patient characteristics. Continuous variables were presented as mean with standard deviation (SD) and range, and frequencies with proportion for categorical variables. Comparison of means was performed by independent t-test, while a Chi-square test was used for comparison of proportions. In case of a small sample size (expected count <5), Fisher's Mid-*P* test was performed. Mean value of each taste quality was compared to normative data [12, 27]. A p-value <0.05 was considered statistically significant. All analysis were performed using SPSS (IBM SPSS Statistics 27.0 for Windows, IBM Corp., Armonk, NY), Stata (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.) and MedCalc's Comparison of means calculator: (https://www.medcalc.org/calc/comparison_of_means.php).

Results

Participants

In total 157 survivors treated for MB/CNS-PNET at OUH were identified during the selected study period. At study start, September 2016, 63 subjects were alive and invited. Figure 1 describes the recruitment of participants. Fifty (79 %) of the survivors consented to participate. Ten were excluded from all testing of

which two were < 10 years at the time of examination, and eight had severe cognitive and/or physical impairment. In total 40 (63.5 %) survivors were examined, and their characteristics are shown in Table 1. Eight out of 40 survivors were only able to conduct the taste test due to the complex olfactory test protocol. Hence, 32 (51 %) survivors were able to be included in the test of smell functions.

Taste function

The results of the 40 survivors who conducted the test of taste function, and also were able to evaluate their own taste function, are listed in Table 1.

Table 1. Characteristics of long-term suvivors treated for MB/CNS-PNET at a young age *(n=40)*

Gender, *n (%)*	
Female	18 (45)
Male	22 (55)
Age at treatment, *mean ± SD (yrs)*	8.4 ± 5.3 (range 0.2- 20)
Age at examination, *mean ± SD (yrs)*	28.9 ± 12.2 (range 10-52)
Follow-up time, *mean ± SD (yrs)*	20.5 ± 11.7 (range 3.5 - 40.4)
Tumor, *n (%)*	
MB*	35 (87.5)
CNS-PNET**	5 (12.5)
Treatment, *n (%)*	
surgery *(yes)*	40 (100)
chemotherapy *(yes)*	32 (80)
irradation *(yes)*	35 (87.5)
Total taste strips score***, *mean ± SD*	10.1 ± 3.9 (range 2-16)
Normogeusia (>= 9)	27 (67. 5%)
Hypogeusia (< 9)	13 (32.5)
Total ageusia (0)	0
Augesia of one or more taste quality***, *n (%)*	9 (22.5)
Sweet	1
Sour	5
Salt	4
Bitter	2
Taste function NRS**** score (0-10), *mean ± SD*	8 ± 1.3 (range 5.5-10)

*MB medullablastoma,**CNS-PNET supratentorial primitive neuroectodermal tumor of the central nervous system,***Score based on Mueller et al. 2003 [27],**** NRS numerical rating scale

The mean value of total test score was 10.1±3.9 (range 2-16). Thirteen (32.5 %) participants scored <9 and were diagnosed with hypogeusia. None of the subjects were diagnosed with complete ageusia, but 9 (22.5 %) were ageusic for one or more taste qualities [27], with sour and salt as the most common ones (Table 1). Mean score of each taste quality is listed and compared with normative values [12, 27] in Table 2. MB/CNS-PNET survivors scored significantly lower on sweet, sour, and salt compared to normative

data (Table 2). Based on NRS (0-10), the mean score of subjective evaluation of taste function was 8 ± 1.3 (range 5.5-10) (Table 1).

Table 2. Participants *(n=40)* mean score of taste qualities compared to normative data [12,27]

	Normative data, *mean (SD)*	MB/CNS-PNET survivors, *mean (SD)*	*p* value
Sweet	3.3 (0.8)	2.9 (1.15)	0.035*
Sour	3.0 (0.8)	2.0 (1.1)	p < 0.001*
Salty	3.1 (0.9)	2.43 (1.4)	0.003*
Bitter	3.0 (1.1)	2.75 (1.2)	0.27

* Statistically significant difference (p values less than 0.05) between MB/CNS-PNET survivors and normative data [12,27]

Smell function

Comparing the TDI-scores with normative data [25], 17 (53 %) survivors were diagnosed with hyposmia. None of the subjects in our study was diagnosed with functional anosmia or as “super smellers”. Participants with hyposmia were compared to subjects with normosomia (Table 3). No significant difference regarding gender, tumor, treatment, age at treatment, age at examination, and follow-up time were found between survivors with hyposmia and those with normosmia. Statistical analysis revealed a significant difference in total TDI-score ($p < 0.001$), THR ($p= 0.018$), DIS ($p = 0.006$), and ID ($p=0.014$) between these two groups.

Although subjects diagnosed with hyposmia had a higher mean NRS score compared to those with normosmia (8 versus 7.7), no statistically significant difference was found between the two groups (Table 3).

Table 3. Participants diagnosed with hyposomia compared to participants regarded as normosomia, (*n=32)*

	Hyposomia**	Normosmia**	p value
Participants, *n (%)*	17	15	
Male, *n (%)*	10 (59)	9 (60)	0.95
Tumor, *n (%)*			
MB***	15 (88)	13 (87)	0.8
CNC-PNET***	2 (12)	2 (13)	
Treatment with radiotherapy, *n (%)*			
yes	16 (94)	12 (80)	0.21
no	1 (6)	3 (20)	
Age at treatment, *mean ± SD (years)*	8.1 ± 4.7	8.5 ± 5.6	0.82
Age at examination, *mean ± SD (years)*	31.2 ± 12.5	28.7 ± 12.3	0.58
Follow-up time, *mean ± SD (years)*	23.1 ± 11.6	20.2 ± 12.5	0.51
TDI-score , *mean SD*	27.4 ± 2.8	32.1 ± 1.1	< 0.001*
Treshold- test, *mean SD*	5.66 ± 1.9	7.1 ± 1.3 (range 3.5-9.25)	0.018 *
Discrimination-test, *mean SD*	10.4 ± 2 (range 5-13)	12.1 ± 0.8 (range 11-14)	0.006 *
Identification- test (1-16), *mean SD*	11.4 ± 1.7 (range 7-13)	12.9 ± 1.4 (range 11-16)	0.014*
Smell function NRS**** score (0-10), *mean ± SD*	8 ± 1.6	7.7 ± 1.4	0.6
Taste strips score, *mean ± SD*	8.9 ± 3.7	11.4 ± 3.6	0.07
hypogeusia, *n (%)*	7 (41)	3 (20)	0.20
normogeusia, *n (%)*	10 (59)	12 (80)	

* Statistically significant (*p* values less than 0.05), ***TDI* score range from 1 to 48: hyposmia > 16.00 - < 30.75 , normosmia ≥ 30.75 - < 41.50 [25]
MB* medullablastoma,*CNS-PNET* supratentorial primitive neuroectodermal tumor , * NRS numerical rating scale

Discussion

This study is the first to evaluate both objective and subjective taste and smell functions in long-term survivors after childhood MB/CNS-PNET. Hyposmia and hypogeusia were found in 53% of 32 survivors, and 32.5% of 40 survivors, respectively. However, the subjective evaluation of taste and smell functions did not reflect the results of objective measurements since the mean score of self-evaluation of both functions were high.

The few published studies regarding taste and smell functions after treatment of brain tumors indicate some alterations in chemosensory functions [20, 21]. Johannesen and coworkers (2002) found reduced taste function in three out of 33 long-term survivors of brain tumor treated ≥ 14 years (median follow up time was 13.1 years), using qualitative examination of taste by identification of the four basic taste qualities [20]. Since they did not describe the test protocol and how they evaluated the results, comparison with our results is difficult [20]. Layrer and coworkers (2013) reported a relatively high degree of taste and smell disturbances 6 weeks after brain irradiation. They used a validated questionnaire, but no objective taste and smell measurements [21]. Since most brain tumor patients receive both RT and chemotherapy [2-4], it is hard to identify which of these treatment modalities may be of most significance when it comes to chemosensory function disturbances [9, 10, 15, 23]. In our study, no significant difference was found between hyposmia and normosmia in survivors treated with or without RT, though it should be mentioned that the number of subjects not receiving RT was small.

More than half (53%) of the participants in our study had a reduced smell function. In comparison, Cohen and coworkers (2014) reported only 3.9% smell dysfunction in a group of 51 survivors of different childhood cancers (including two MB survivors) with a mean follow-up time of 12.4 years [18]. IJpma and

coworkers (2016) found no difference in smell function in testicular cancer survivors compared to a control group [19]. However, cooperation and patient attention throughout all three subtests of the Sniffin' Sticks test [29] may be specifically challenging in brain cancer survivors. Even though severe cognitive and functional impaired survivors were excluded in the present study, the proportion of participants with reduced chemosensory functions may be high due to the vast variation in cognitive function after cancer treatment. Stadskleiv and coworkers (2020) have shown that cognitive function after treatment may vary considerable in MB/CNS-PNET survivors [24]. In another study, 60% of MB/CNS-PNET survivors had learning or memory problems compared to only 3% in a comparison group [1]. This is important since cognitive function may have a significant influence on olfactory testing, especially the identification and discrimination tests [28]. However, no such influence was observed on the olfactory threshold test [28], thereby emphasizing the importance of including a threshold test when assessing olfactory function in MB/CNS- PNET survivors. Additionally, there may be a cultural difference in odor detection, as showed in a Danish validation study of Sniffin' Sticks [30]. They found that the original Sniffin' Sticks (Burghart, Wendel, Germany) were not applicable in Denmark since several of the odors in the test were unfamiliar to the population [30].

The participants in our study recorded a high mean score in self-evaluation of smell function. This is in accordance with a study on HNC patients, 3 months after RT, where the patients subjectively did not notice smell dysfunction even though there was a significant reduction in olfactory function during RT [31]. Self-rating of olfactory function has been shown to have low reliability even in healthy subjects [32], thus a validated objective measurement is recommended when assessing smell function [32, 33].

In our study, 32.5% of survivors were diagnosed as hypogeusic. This is quite similar to the results reported in the previously mentioned study on survivors of different childhood cancers, were they found 27.5% with taste dysfunction using 25 sample sipping test [18]. In the study by IJpma and coworkers (2016) impaired taste function was also found in testicular cancer survivors compared to a control group [19]. As mentioned, both Cohen and coworkers (2014) and IJpam and coworkers (2016) found only a reduced taste function with no reduction in smell function. This is in conflict with other studies, in which solitary taste dysfunction is less frequent than smell impairment, most often patients complaining of taste impairment actually have an olfactory deficit [10, 35-37].

None of the participants in our study was found to be complete ageusic. This is in accordance with results from other studies showing that complete ageusia is a rare condition [34, 35]. To differentiate "objectively" between hypogeusic and ageusic is difficult as revealed by Falk and coworkers (2013). Thus, the use of taste strips may be limited to differentiate between "healthy" and "non-healthy" subjects [34]. It should be mentioned that clinical assessment of taste function needs a multifactorial approach including evaluation of the patient's complaints/symptoms, local oral morphology (e.g. papillae), infections, saliva function, dental status, and use of any medication [10, 14]. The mean NRS score of 8 indicated that most of the survivors in the present study did not notice or were aware of impaired taste function.

Compared to normative data [27] the MB/CNS-PNET survivors in our study showed a significant lower value for the taste qualities sweet, sour, and salt. In a study with breast cancer patients, a significant lower value of sour quality on the left side of the tongue was found [12]. In our study, 22.5% of the survivors where ageusic to one or more taste qualities, with sour and salt being the most frequent quality lost. In HNC survivors salt was also found to be one of the most impaired taste qualities, in addition to bitter [38]. Impaired taste qualities may affect diet and nutritional status. A reduced intensity of different taste qualities, like for instance salt, may influence on nutritional behavior and may be associated with increased body mass index [39]. Barbosa da Silva and coworkers (2019) found that RT affected sweet, bitter, and sour sensitivities in HNC patients [15]. However, there may be genetic variations in taste receptors that may influence diet and nutritional behavior, and risk of different diseases [40, 41]. In a Caucasian population, 25% was found to be non-tasters of compounds containing the thiocyanate group responsible for bitter taste [40, 42]. There is also a risk for misidentifying a taste quality, referred to as “taste confusion” [43]. A study on 1000 participants with different health status sour-bitter confusion was reported to be the most common, while confusion involving the sweet quality was rare [43].

A strength of the present study was the use of objective validated tests for both taste and smell functions, and the inclusion of all three subtests for the evaluation of smell function. The study population was homogenous and relatively large compared to other studies in the literature, and additionally the exceptionally long median follow-up time of over 20 years. An important limitation is the lack of a matched control-group. Due to the vide spread in participants age at study start, the participants were not divided into age and gender groups when the results were compared to normative data. There is a significant correlation between taste function and subjects’ age and gender, showing decreased taste with age and women exhibiting higher taste score than men regardless of age [26]. Furthermore, reduced olfactory function can result from aging [14]. However, the main drop in olfactory identification ability occur in the sixth and seventh decades of life [14], and none of our participants was in that age group. In addition, no significant difference was found between those with hyposmia and normosmia related to age at treatment, age at examination or follow-up time. Even though the present study revealed objective taste and smell dysfunctions, the mean score of subjective evaluation was high and did not reflect the objective findings. In addition to a NRS scale a validated patient-reported questionnaire as used by Layrer and coworkers (2014) [21], would have gathered a broader insight to subjective evaluation.

In conclusion, a high prevalence of taste and smell impairments was found in survivors of childhood MB/CNS-PNET many years after treatment. Interestingly, most survivors did not report impaired functions themselves. Nonetheless, reduced taste and smell functions may still have severe impact on everyday life including diet, health, and risk of nutrition related diseases. The medical team should have knowledge of these possible long-term effects. This highlights the importance of including taste and smell measurements in cancer patients to gain knowledge on treatment modalities for those who suffer chemosensory impairment after cancer therapy.

Declarations

Acknowledgment

We would like to thank the survivors and their families for participating in this study. The authors' would also like to thank Dr. Mette Bratt and her team at St Olavs hospital. Unfortunately, Dr. Bratt deceased before this article was submitted. Thanks to Ragnhild Sørum Falk for assisting with statistical analyses. We would also like to thank the research nurses Elna Hamilton Larsen and Karin Sylte Hammeren for their assistance during the study.

Declarations

Not applicable

Funding

The Pediatric Research Foundation at OUH, the Norwegian user organizations "Hjernesvulstforeningen» and «Støtteforeningen for kreftrammede» supported this study financially.

Conflicts of interest

There are no conflicts of interest.

Data and material availability

Can be available from corresponding author if requested.

Code availability

Not applicable

Authors' contributions

Optional/Not applicable

Ethical considerations

The Regional Committee approved the study for Medical Research Ethics (2015/2362REK sør-øst B), Health Region South-Eastern Norway. The study was registered in ClinicalTrials.gov (NCT02851355). Ethical standards of Declaration of Helsinki were followed.

Consent to participate

Informed consent was obtained from all participants and/or their parents/guardians.

Consent for publication

Not applicable

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Figures

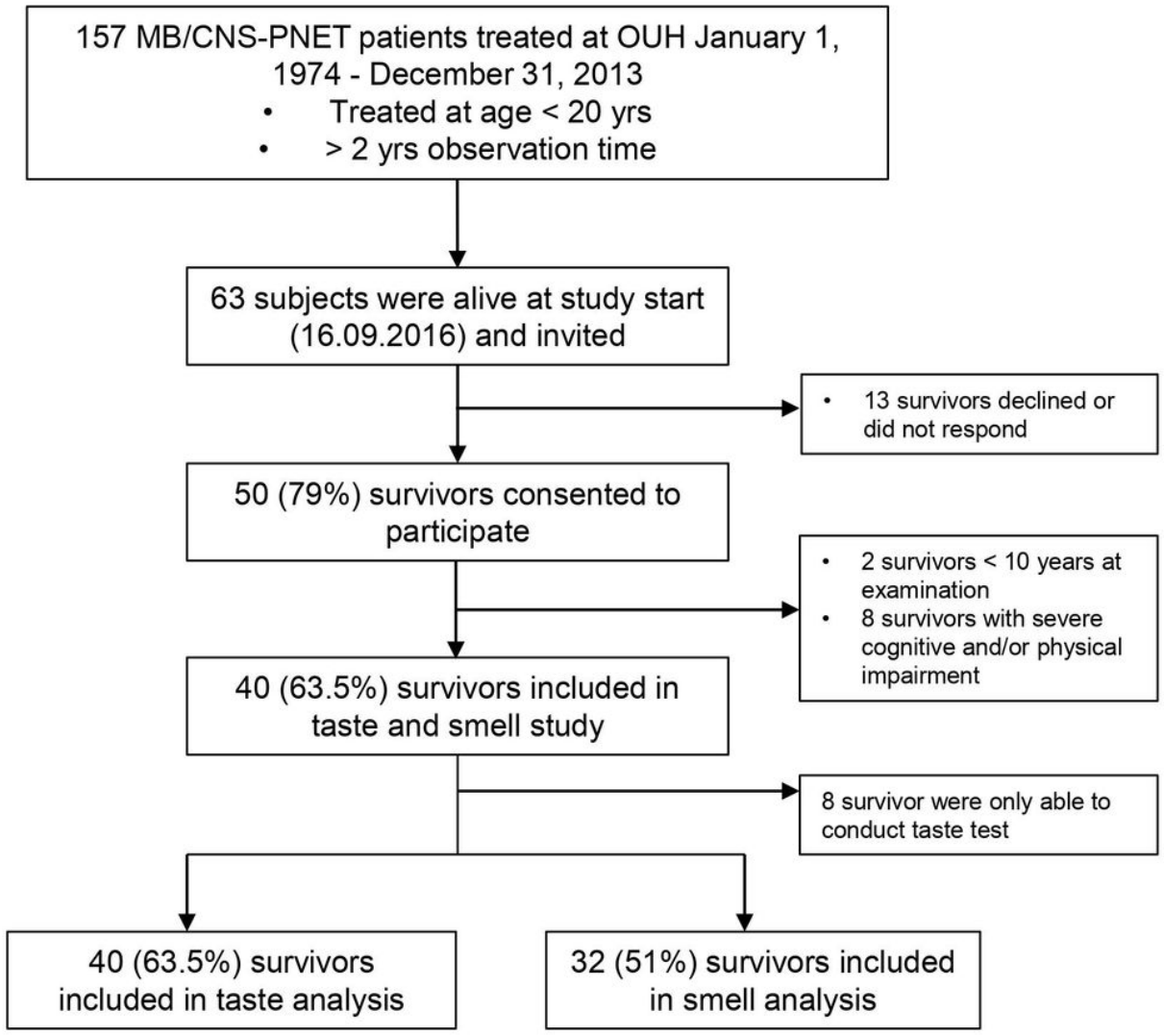

Figure 1

Flowchart of recruitment of study population

Abbreviations: *MB* medulloblastoma, *CNS-PNET* supratentorial primitive neuroectodermal tumor, *OUH* Oslo University Hospital