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Taste and Smell Disturbances after Brain Irradiation: A Dose Volume Histogram Analysis of a Prospective Observational Study

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Abstract

Purpose—Radiation-induced taste and smell disturbances are prevalent in patients receiving brain radiotherapy, although the mechanisms underlying these toxicities are poorly understood. We report the results of a single institution prospective clinical trial aimed at correlating self-reported taste and smell disturbances with radiation dose delivered to defined areas within the brain and nasopharynx.

Methods and Materials—22 patients with gliomas were enrolled on a prospective observational trial in which patients underwent a validated questionnaire assessing taste and smell disturbances at baseline, and at 3 and 6 weeks after commencement of brain radiotherapy. 14 patients with glioblastoma, 3 patients with grade 3 gliomas, and 5 patients with low grade gliomas participated. Median dose to tumor volume was 60 Gy (range 45–60 Gy). Dose volume histogram (DVH) analysis was performed for specific regions of interest (ROI) that were considered potential targets of radiation damage including the thalamus, temporal lobes, nasopharynx, olfactory groove, frontal pole and periventricular stem cell niche. The %v10 (percent of ROI receiving 10 Gy), %v40, and %v60 were calculated for each structure. Data from questionnaires and DVH were analyzed using stepwise regression.

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Conflicts of Interest: None

Results—20 of 22 patients submitted evaluable questionnaires that encompassed at least the entire radiotherapy course. 10 of 20 patients reported experiencing some degree of smell disturbance during radiotherapy, and 14 of 20 patients experienced taste disturbances. Patients reporting more severe taste toxicity also reported more severe toxicities with sense of smell ($r2=0.60$, $p<0.006$). Tumor location in the temporal lobe predicted for increased severity of taste toxicity ($F3, 16=1.44$, $p<0.06$). The nasopharynx was the only structure in which the DVH data predicted the presence of radiation-induced taste changes ($r2=0.28$, $p<0.02$).

Conclusions—Radiation-induced taste toxicity appears to be more common in temporal lobe tumors, and may be related to the dose received by the nasopharynx.

Introduction

Brain irradiation is delivered to approximately 200,000 patients a year for either cancerous or benign brain tumors(1). Among the underreported toxicities that patients who receive brain irradiation experience are alterations in the senses of taste and smell. These toxicities are poorly understood, but can be chronic in nature and can affect patients' quality of life during and after treatment. A major controversy with regard to radiation-induced taste alterations is the mechanism by which this dysfunction occurs. Taste alteration, or dysguesia, can be seen in patients receiving radiotherapy to the oral cavity and oropharynx after doses of 60 Gy(2). However, patients with brain tumors receive only a fraction of this dose to these regions. Mechanisms for brain tumor patients experiencing dysguesia are unknown. One theory is that scatter radiation affects the function of the salivary glands and tissues in the nasopharynx. A competing theory is that the olfactory stem cells within the brain are depopulated by radiation.

In 2010, a pilot study was undertaken to prospectively determine if a mechanism for radiation-induced taste dysfunction could be elucidated via qualitative assessment of patient's taste and smell during and after brain radiotherapy. The study attempts to correlate taste and smell outcomes with tumor location and the doses delivered to potential target structures. The goal of this study was to analyze archived radiation dose maps for each patient enrolled on this pilot study to determine if the doses of radiation received by certain structures could predict the presence or degree of taste and smell disturbances after radiotherapy.

Materials and Methods

Data Acquisition and Patient Characteristics

This study was approved by our institution's Institutional Review Board. Patients with a pathologically-proven glioma who were to be treated with external beam radiotherapy were offered enrollment on this prospective observational trial. Between May, 2009 and April, 2010, twenty-two patients were enrolled. Inclusion criteria for the study included normal baseline self-reported taste perception, and at least 6 month expected survival. Two patients were excluded from the final analysis because of inability to complete follow-up questionnaires. Patients' radiotherapy consisted of either 3D conformal radiotherapy (n=17)

or intensity modulated radiotherapy (n=3). Dose fractionation was 1.8 Gy/fraction (n=8) or 2.0 Gy/fraction (n=12). Patient characteristics are summarized in Table 1.

Regions of Interest (ROI) Selection and Delineation

The putative targets of radiation damage assessed in this study were selected based on the known or hypothesized function of the regions. The subventricular stem cell niche is a region of adult neurogenesis and the origin of olfactory stem cells. The olfactory bulb is the destination of migration of olfactory stem cells(3). The thalamus and frontal poles play a role in cerebral processing of gustatory information in primates and humans(4). The nasopharynx is the location of chemoreceptors that contribute to olfaction.

ROI boundaries used standard anatomical landmarks and are illustrated in Figure 1. Briefly, the subventricular stem cell niche was drawn along the caudate nucleus and ventricle. The frontal pole's posterior border was drawn anterior to the corpus callosum; the inferior border was superior to the orbit. The superior border of the thalamus was determined by inferior border of the lateral ventricles and the inferior border was determined by locating the cerebral peduncles and beginning the thalamus one slice superior to it. The olfactory bulb was estimated based on the location of the cribiform plate on CT imaging.

Dosimetry

Delineation and dose volume histogram (DVH) analysis of ROI were performed using the Pinnacle treatment planning system (Philips, Andover, MA). Prior to ROI delineation, the pre-treatment Magnetic Resonance Imaging (MRI) and treatment planning Computed Tomography (CT) image sets were fused. After ROI were delineated, doses from the archived treatment plan were restored. DVH analysis determined the volume of each ROI received at each corresponding dose (v10, v40, and v60). Because of variability in brain volumes and ROIs, structural dosimetry was normalized by determining the percentage of each structure that received the dose of interest (%v10, %v40, %v60).

Toxicity Outcomes

Toxicity outcomes were based on validated questionnaires assessing taste and smell disturbances(5). Sample questionnaire is presented in Figure 2. Participants were asked to rate their individual taste and smell abnormalities for five questions addressing self-perceived changes as "insignificant," "mild," "moderate," "severe,", or "incapacitating." The tool yields a taste complaint score (0–14) on the basis of subject responses to questions addressing changes to the sense of taste. One point is added for each reported specific taste complaint (e.g., sweet, salty, sour, bitter) and two points for a rating of "severe" or "incapacitating" for any question. Similarly, a smell complaint score (0–9) was generated by adding one point for a positive response to each of five questions with two points assigned to a severity rating of "severe" or "incapacitating". Patients completed questionnaires at baseline, and then at 3 and 6 weeks after commencement of brain radiotherapy.

Statistics

Because of the small number of patients and the multiple questionnaires completed by each patient, the maximum toxicity score for either the 3 or 6-week assessment of taste and smell

toxicity was used for statistical considerations. Stepwise logistic regression (SPSS17.0) was used to determine the percent of ROI dose that predicted for the maximum value of taste and smell toxicity as measured by the questionnaires. One-way analysis of variance (ANOVA) was used to determine if a relationship existed between tumor location (frontal, parietal, subcortical, or temporal) within the brain and the maximum toxicity value for taste or smell toxicity as measured by the questionnaires.

Results

Taste Outcomes

Taste and smell outcomes are shown in Table 2. Of the 20 responding participants, median taste toxicity score prior to therapy was 0 (range 0–5). Five patients (25%) reported no abnormalities in taste after completion of radiotherapy. 11 of 20 respondents (55%) reported an increase in taste disturbance as compared to their baseline (pre-radiotherapy) score. Median taste toxicity score at 3 and 6 weeks after commencement of radiotherapy was 2 (range 0–9) and 3 (range 0–10), respectively. Median worst score for taste toxicity during radiotherapy was 3.

Smell Outcomes

Of the 20 responding participants, median smell toxicity score prior to therapy was 0 (range 0–4). Twelve patients (60%) reported no abnormalities in smell after completion of radiotherapy. 7 of 20 respondents (35%) reported an increase in smell disturbances as compared to their baseline score. Median smell toxicity score at 3 and 6 weeks after commencement of radiotherapy was 0 (0–4) and 1 (0–5), respectively. Median worst score for smell toxicity during radiotherapy was 0.5.

Six of six participants who reported no taste abnormality also reported no smell abnormality. Furthermore, ten of ten patients who reported a smell abnormality also reported a taste abnormality.

Predictive Factors

Table 3 depicts dosimetric data for ROI. Stepwise Regression analysis was used to determine ROIs that predicted taste and smell toxicity scores independently at an individual volume dose (%v10, %v40, and %v60). Due to the small sample size and limited toxicity responses to the questionnaire, no ROI predicted smell abnormalities. The %v10 of the nasopharynx was predictive of taste abnormalities (r^2= 0.28, $p<0.02$). The beta value indicated an increased in abnormality severity was associated with a larger percentage of ROI volume exposed to the corresponding dose. Patients reporting more severe taste toxicity also reported more severe toxicities with sense of smell (r^2=0.60, $p<0.006$).

Analysis of variance was used to determine if tumor location within the brain correlated to taste or smell disturbances as measured by questionnaires. Tumor location in the temporal lobe predicted for increased severity of taste toxicity ($F_{3, 16}$=1.44, $p<0.06$). Temporal lobe tumors showed a greater degree of taste toxicity when compared to frontal lobe ($p<0.04$) and

parietal lobe ($p<0.02$) tumor locations. No statistically significant location (one-way ANOVA) was found for tumor location and severity for abnormality of smell.

Discussion

Toxicity related to the senses of taste and smell after brain radiotherapy is poorly understood, though it is important because it can contribute to the nutritional status of patients during a metabolically stressful period. The majority of data related to abnormalities in the sense of taste after radiation therapy is in the population of patients who received radiotherapy for cancers of the head and neck region. In these patients, the likely mechanism of the toxicity relates to direct damage to receptors within the tongue as the doses received by these regions can be in the range of 50–70 Gy and toxicity has been associated at doses beyond 30 Gy to the oral cavity(6). With brain irradiation, however, there is a significantly lower dose delivered to regions within the tongue, and as such, the mechanisms of taste disturbances are likely different. There is virtually no published data on the incidence of radiation-induced dysguesia after brain radiotherapy. A single prior series from the National Hospital in Oslo, Norway has previously reported that 3 of 33 patients experienced late dysguesia as a result of brain radiotherapy(7). The incidence of toxicity in the Norwegian series is different from the current study in that it assessed patients retrospectively, assessed patients for late/permanent toxicity at a nonstandardized time point, and did not use a validated toxicity scale. In the current study, toxicity was assessed regularly during brain radiotherapy using a validated measure for taste and smell abnormalities(5). As such, this series represents the first prospective study in the scientific literature to document the natural history of radiation-induced dysguesia after brain radiotherapy for primary brain tumors.

There have been several proposed mechanisms by which such radiation-induced dysguesia can occur after brain radiotherapy: 1) depletion of neural progenitor cells, 2) damage to central neural pathways, 3) depletion of sensory cells by scatter or exit radiation dose, 4) damage to sensory mechanisms. The goal of the current study was to determine if doses to any of the putative targets of radiation damage could predict for functional outcome in patients. To this end, this study performed dose volume histogram analyses of several potential target structures and subsequently correlated findings to results of patient questionnaires. Recent data suggests that irradiation of various structures within the brain can lead to declines in specific cognitive functions(8), though such a study has never been performed for taste and smell disturbances. In a series presented by XXXX et al, a 40 Gy dose threshold was found to be sufficient to lead to detectable changes in several cognitive tests in a population of patients with primary brain tumors. This dose threshold to normal brain tissue was the rationale for assessing the v40 dose level in this study. V10 was considered to be suggestive of a mechanism for depletion of stem cells given their exquisite sensitivity to radiation(9). V60 was considered to be the threshold for radiation necrosis of brain tissue as previously reported by Emami(10).

The data from the current study suggests a possible mechanism for the radiation-induced dysguesia after brain radiotherapy related to damage to sensory cells within the nasopharynx. The fact that all patients who reported a smell abnormality also reported a taste abnormality supports the suspicion that these senses were interrelated and that toxicity

with smell contributed to corresponding toxicity with taste. Patients with temporal lobe tumors experienced a greater likelihood of radiation-induced taste and smell disturbances in the current study. Furthermore, radiation dose to the nasopharynx was the only structure for which DVH data showed a relationship to toxicities with the senses of taste and smell. Given the anatomic proximity between the temporal lobes and nasopharynx, these findings would suggest that the dose to the nasopharynx or directly adjacent structures represent the critical target for the development of taste and smell disturbances after brain radiotherapy.

There were several limitations of this study. The patient numbers were small, preventing a more robust statistical analysis. Furthermore, the patients all underwent chemotherapy, which could be a confounding factor given its ability to deplete various cell types. Finally, it is possible that having a tumor in the temporal lobe, because of its proximity to the nasopharynx, may cause a higher radiation dose to be delivered to the nasophaynx, thus leading to an apparent dose relationship between toxicity and dose delivered within the nasopharynx. As such, the results of this analysis cannot rule out a potential target of toxicity within the temporal lobe. Further prospective studies are necessary in order to corroborate the results of the current study. Future directions for this research may include the possibility of interventions to prevent toxicity whether it be with cytoprotective agents or the limiting of dose to target structures when feasible. A prospective study in which the %v10 in the nasopharynx is limited and taste outcomes are collected would be the next step to determine if taste outcomes can be improved by constraining the dose to the nasopharynx. Finally, the impact of chemotherapy effects on taste and smell disturbances after brain radiotherapy remains to be elucidated.

Conclusion

Radiation-induced taste toxicity appears to be more common in temporal lobe tumors, and may be related to the dose received by the nasopharynx.

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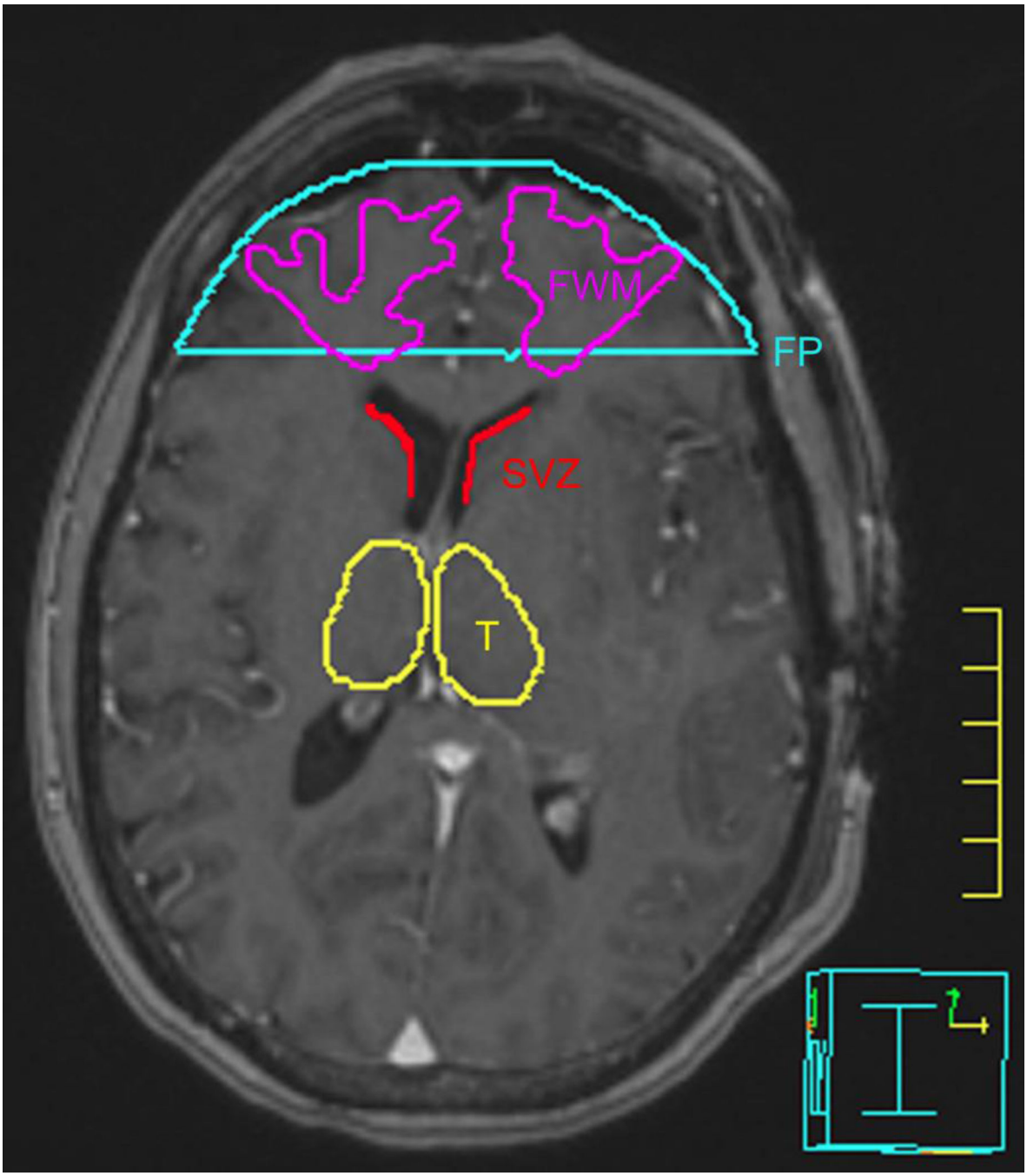

Figure 1.

Region of Interest Delineation. 1A. T1-weighted axial view MRI of the brain with frontal pole (FP), frontal white matter (FWM), subventricular stem cell niche (SVZ), and thalamus (T).

Taste and Smell Questionnaire

Taste Complaints: Please rate

Questions	Insignificant	Mild	Moderate	Severe	Incapacitating
I have noticed a change in my sense of taste					
A food tastes different than it used to					
I have a persistent bad taste in my mouth					
Drugs interfere with my sense of taste					
I would rate my abnormal sense of taste as					

Taste Complaints: Answer "yes" or "no"

Questions	Yes	No	If "Yes" then:
I am experiencing an abnormal sensitivity to salt			Salt tastes: Stronger___ or Weaker ___
I am experiencing an abnormal sensitivity to sweet			Sweet tastes: Stronger ___ or Weaker ___
I am experiencing an abnormal sensitivity to sour			Sour tastes: Stronger ___ or Weaker ___
I am experiencing an abnormal sensitivity to bitter			Bitter tastes: Stronger ___ or Weaker ___

Smell Complaints: Please rate

Questions	Insignificant	Mild	Moderate	Severe	Incapacitating
I have noticed a change in my sense of smell					
A food smells different than it used to					
Specific drugs interfere with my sense of smell					
I would rate my abnormal sense of smell as					

Smell Complaints: Answer "yes" or "no"

Questions	Yes	No	If "Yes" then:
I have an abnormal sensitivity to odors			Odors are: Stronger___ or Weaker ___

Figure 2.

Sample Taste and Smell Questionnaire. 1 point was added for each complaint. 1 additional point was added for each complaint that was rated as either “severe” or “incapacitating”. Taste toxicity score was calculated based on a maximum score of 14. Smell toxicity score was calculated based on a maximum score of 9.

Table 1

Patient characteristics

	Number (range)
Patients	20
Median Age	58 (19–78)
Sex	
Female	9
Male	11
WHO Grade	
II	5
III	2
IV	13
Tumor Location	
Frontal	11
Temporal	5
Parietal	3
Occipital	1
Tumor Side	
Left	7
Right	13
Median Radiation Dose	60 Gy (45–60 Gy)
Radiation Fractionation	
1.8 Gy/fraction	8
2.0 Gy/fraction	12
Radiation Modality	
3D Conformal	17
IMRT	3

Table 2

Individual Patient Toxicity Data

Patient	Complaint Score						Tumor Location	Maximum Dose (Gy)	Dose per fraction
	0 weeks		3 weeks		6 weeks				
	taste	smell	taste	smell	taste	smell			
1	1	0	4	3	4	4	Left Parietal	60	2.0
2	0	0	0	0	3	0	Right Frontal	59.4	1.8
3	0	0	2	1	0	0	Right Frontal	45	1.8
4	0	0	1	3	1	3	Right Temporal	60	2.0
5	4	0	0	0	3	0	Left Occipital	60	2.0
6	0	0	1	0	6	3	Left Temporal	60	2.0
7	5	1	7	0	5	0	Right Temporal	60	2.0
8	5	0	5	4	5	4	Left Frontal	54	1.8
9	1	0	9	3	10	5	Left Temporal	60	2.0
10	2	0	0	0	0	0	Left Parietal	60	2.0
11	0	0	3	2	3	2	Left Temporal	60	2.0
12	0	0	3	0	4	0	Right Frontal	59.4	1.8
13	0	0	0	0	1	0	Right Frontal	54	1.8
14	0	1	4	0	2	1	Right Frontal	54	1.8
15	0	0	0	0	0	0	Right Frontal	60	2.0
16	3	4	4	5	3	0	Right Frontal	54	1.9
17	0	0	5	3	5	3	Right Frontal	60	2.0
18	0	0	1	0	1	0	Right Parietal	59.4	1.8
19	4	1	0	0	0	0	Right Frontal	60	2.0
20	0	1	0	0	0	0	Right Frontal	60	2.0

Table 3

Individual Patient Dosimetric Data

Patient	Thalamus		Temporal Lobes		Nasopharynx		Olfactory Bulb		Frontal White Matter		Frontal Poles		Stem Cell Niche	
	%v10	%v40	%v10	%v40	%v10	%v40	%v10	%v40	%v10	%v40	%v10	%v40	%v10	%v40
1	1	0.04	0.56	0.36	0	0	0	0	0.16	0	0.16	0	1	0.04
2	1	1	0.99	0.05	0	0	0.92	0	1	1	1	0.98	1	1
3	0.69	0.03	0.32	0	0	0	0	0	0.76	0.48	0.69	0.29	0.86	0.4
4	1	0.69	0.71	0.50	0.23	0	0.43	0	0.65	0.17	0.53	0.01	1	0.69
5	1	0.59	0.94	0.20	0	0	0	0	0.54	0	0.42	0	1	0.07
6	1	0.53	0.97	0.58	0.88	0	1	0	0.71	0.54	0.46	0.15	1	0.47
7	1	0.50	0.66	0.50	0.25	0	0.57	0	0.49	0	0.29	0	0.84	0.35
8	1	0.93	0	0	0	0	0	0	0.93	0.60	0.81	0.44	1	1
9	1	0.64	0.86	0.36	0.68	0	0.41	0.04	0.83	0.31	0.72	0.19	1	0.51
10	1	0.73	0.74	0.21	0	0	0	0	0.01	0	0.01	0	0.94	0.03
11	1	0.55	0.85	0.45	0.92	0	0.87	0.01	0.61	0.28	0.58	0.18	1	0.51
12	1	0.34	0.85	0.17	0	0	1	0.99	1	1	1	1	1	1
13	0.40	0.01	0.27	0	0	0	0	0	0.86	0.32	0.83	0.31	1	0.51
14	1	0.71	0.82	0.39	0.85	0.05	1	0.36	0.71	0.37	0.63	0.14	1	0.86
15	1	1	1	1	0	0	1	0.86	1	1	1	1	1	1
16	1	0.67	0.28	0	0	0	1	0	1	0.83	1	0.78	1	1
17	0.99	0	0.99	0.45	0.99	0	1	0.10	1	1	1	0.98	1	1
18	0.84	0	0.19	0	0	0	0	0	0.67	0	0.64	0	0.97	0
19	1	1	1	0.42	0	0	1	0.33	1	0.22	0.89	0.15	1	1
20	1	1	1	0.52	0	0	0.95	0.01	1	0.73	1	0.28	1	1