CHAPTER FIVE
RESULTS AND ANALYSIS

5.0 OVERALL SURVIVAL RATE

The 39 patients were examined at regular follow-up clinic visits. Within this group of 39 patients, the overall observed survival (living with or without disease) at 2 years, was 88 % and at 5 years was 55 %.

5.1 TCP CALCULATIONS USING BIOPLAN WITH RESPECT TO TREATMENT PLANNING TECHNIQUE

Of the 39 patients who were eligible for this study, only 13 patients had three-dimensional treatment plans, while the rest had two-dimensional plans.

5.1.1 TCP CALCULATIONS FOR PATIENTS WITH THREE-DIMENSIONAL PLANS

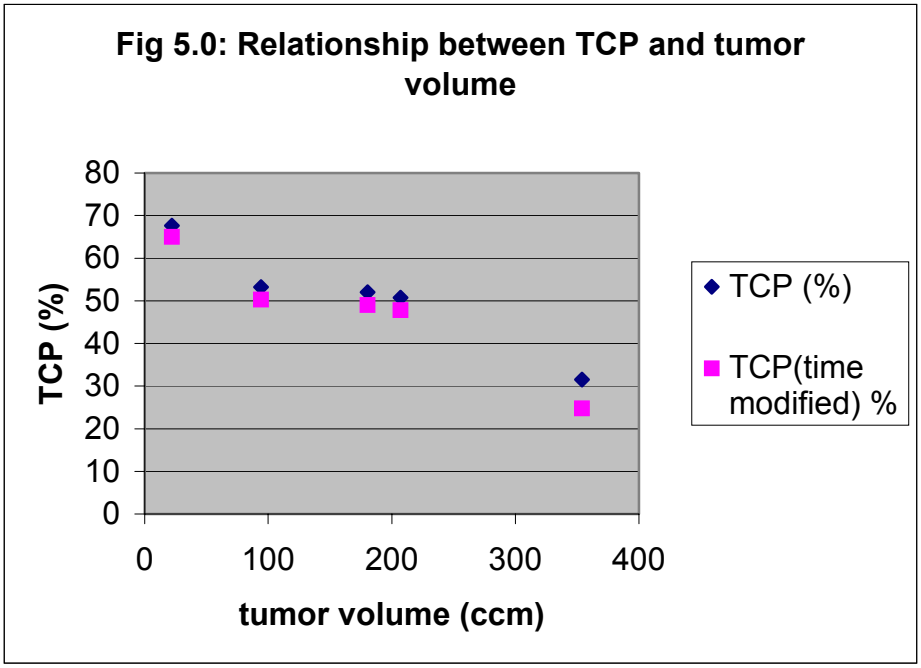
By transferring DVH files from the HELAX TMS treatment planning system to the BIOPLAN software, the calculation of TCP for patients for three-dimensional plans was performed. Patients who had three-dimensional plans were sorted into two groups namely, those who received a total dose of 54 Gy and those who received a total radiation dose other than 54 Gy. The results of TCP calculations of the 5 patients with three-dimensional plans who were given a radiation dose of 54 Gy are shown in Table 5.0.

Table 5.0: Shows the calculated values of TCP at different volumes for a total radiation dose of 54.0 Gy.

DOSE (Gy)	TUMOR VOLUME (ccm)	TCP (%)	TCP(time modified) %♣
54.0	22.0	67.6	65.0
54.0	94.2	53.2	50.3
54.0	180.5	52.0	49.0
54.0	207.0	50.7	47.8
54.0	354.0	31.5	24.8

Below is a scatter graph showing how tumor control probability varied with tumor volume for the same values in Table 5.0.

♣ TCP (time modified) means the calculated TCP taking tumor proliferation into consideration

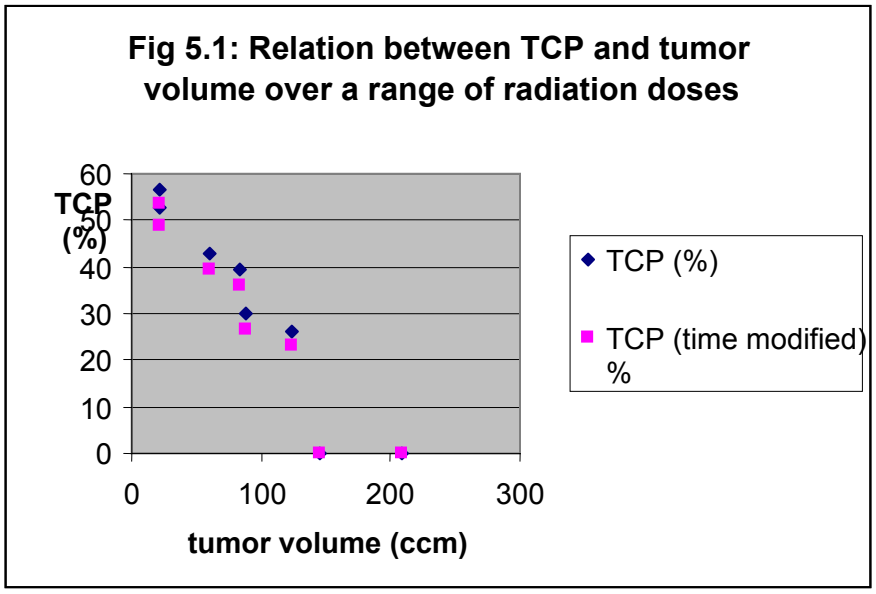


TCP values were also calculated over the range of total radiation dose delivered to 8 patients with three-dimensional plans and the results are shown on the Table below.

Table 5.1 Shows results of TCP calculations over a range of doses.

DOSE (Gy)	VOLUME (ccm)	TCP (%)	TCP (time modified) %
30.0	146	0.0	0.0
45.0	22.0	56.4	53.6
46.8	22.0	52.5	49.0
49.8	87.5	30.0	26.5
49.8	123.2	26.2	23.0
50.0	61.0	42.9	39.5
50.0	83.4	39.4	36.1
50.4	209	0.0	0.0

Results from Table 5.1 were plotted on a scatter plot graph and yielded Fig 5.1 as shown below.



5.1.2 TCP CALCULATIONS FOR PATIENTS WITH TWO-DIMENSIONAL PLANS

The tumor volume for patients with two-dimensional plans was estimated from the dimensions of the set field size used to treat the particular patient. For example, for a patient treated using two isocentric fields namely a 6 cm x 9 cm right anterior oblique field and a 11 cm x 9 cm left anterior oblique field, the tumor volume was determined from the geometric boundaries of the set treatment fields i.e. 9 cm x 11 cm x 6 cm . This is an overestimation of the "tumor volume" because the treated volume included normal tissue around the tumor.

As a result of this method used, the tumor volume of the two2-dimensional plans was in most cases very large when compared with the tumor volumes obtained from three-dimensional plans resulting in predictably low TCP values. An approximation of the patient tumor DVH was estimated from the prescribed percentual tumor dose (TD) and the calculated percentual maximum tumor dose (TD_{max}). In these cases the prescription dose was selected from the minimum isodose line covering the tumor volume on each

computer tomography (CT) slice, and represented the minimum dose received by the tumor. The general shape of the DVH is as shown in Fig. 5.2.

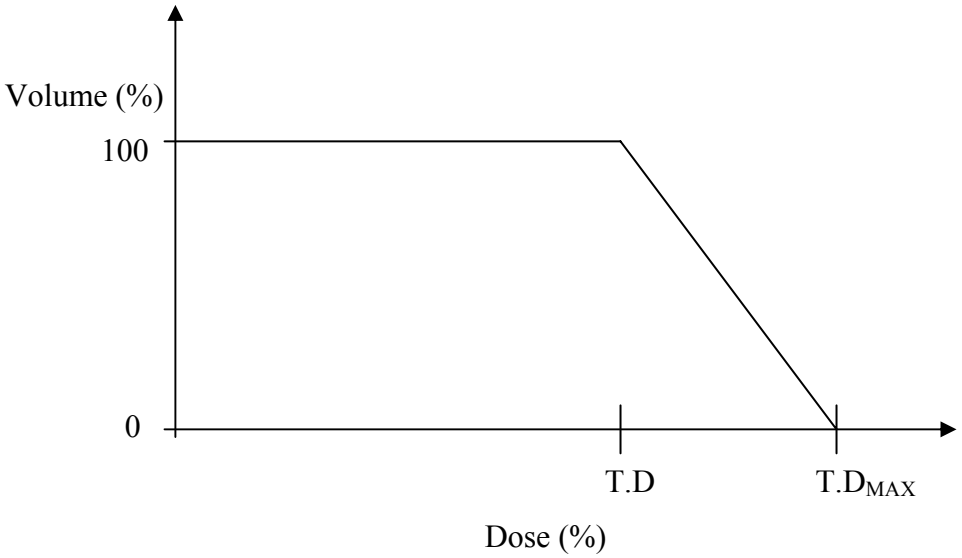
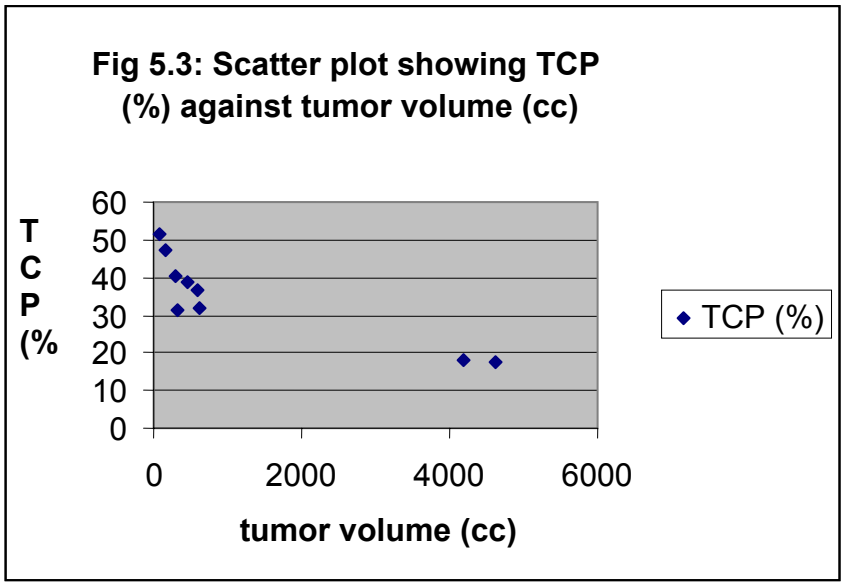


Fig 5.2: Shows the typical shape of a DVH

Table 5.2: Shows TCP and tumor volume values for 9 patients who had two-dimensional treatment plans and were radiated to 54.0 Gy.

DOSE (Gy)	VOLUME (ccm)	TCP (%)
54.0	82.2	51.5
54.0	160.0	47.1
54.0	300.4	40.6
54.0	318.5	31.5
54.0	460.0	39.0
54.0	607.5	36.4
54.0	620.0	31.6
54.0	4200.0	18.3
54.0	4620.0	17.6

These results were plotted on a scatter plot graph as shown in Fig 5.3.

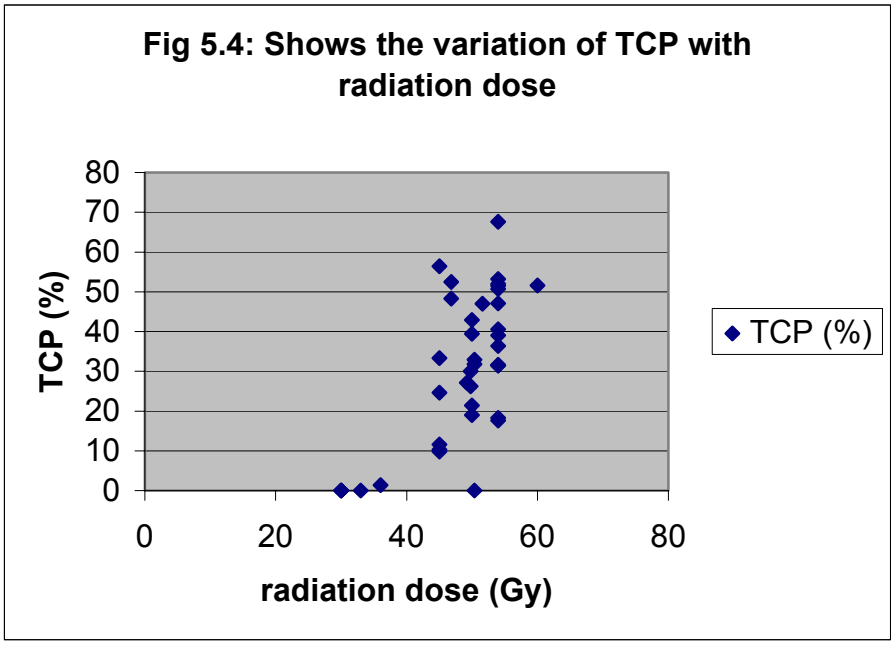


Calculations of TCP were further done at appropriate prescription doses and relevant tumor volumes as determined from the treatment files for the other 17 patients who had two-dimensional treatment plans.

Table 5.3: Shows TCP and tumor volume values for 17 patients treated using two-dimensional treatment plans over a range of total radiation dose.

DOSE (Gy)	VOLUME (ccm)	TCP (%)
30.0	140.0	0.0
30.0	164.5	0.0
33.0	152.0	0.0
36.0	138.4	1.4
45.0	132.4	33.3
45.0	216.0	24.6
45.0	234.0	11.6
45.0	514.5	10.3
45.0	612.0	9.8
46.8	121.2	48.3
49.2	113.0	27.1
50.0	560.0	21.4
50.0	755.0	19.0
50.4	252.0	32.9
50.4	392.5	31.8
51.6	318.5	47.0
60	580.5	51.6

A scatter graph was plotted for the whole patient population to establish the relationship between TCP and radiation dose as shown in Fig 5.4.

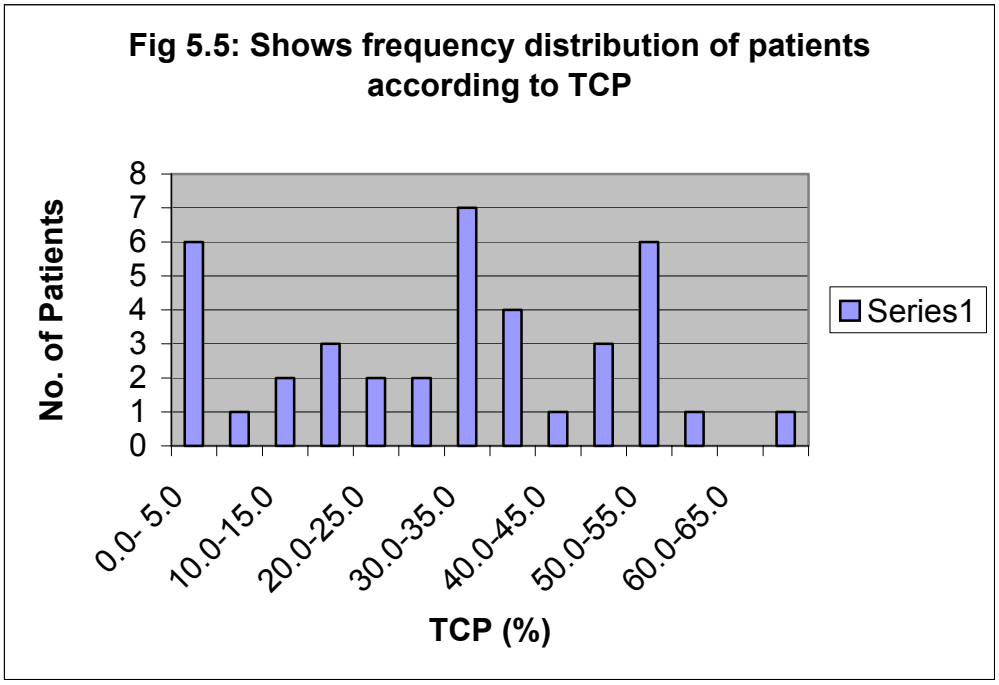


The general shape of TCP versus radiation dose graph is sigmoidal, which is not exhibited in the above graph. A Boltzmann sigmoidal fit was done to the data using Origin® 6.1 which is a Windows® - based scientific graphing and data analysis software and the coefficient of correlation was found to be equal to 0.46722, which means the data fell short of obeying a sigmoid function. It is worth mentioning that despite not getting the sigmoidal curve, the results still show that TCP increased with radiation dose, which was expected. The shape of the scatter graph could be explained as follows

1. The TCP values calculated were at times for different tumor volumes for the same prescribed radiation dose. There was no indication of a trend of prescribing a certain dose based on a given tumor volume range.
2. A larger number of patients may produce the expected sigmoidal curve.

5.2 OVERALL MEAN TUMOR CONTROL PROBABILITY

The figure below is a frequency distribution of the TCP values for the whole group of 39 patients treated as calculated using the software BIOPLAN. The overall mean TCP was calculated to be 31 %.



The spread in TCP values can be attributed to a combination of different tumor volumes, different prescription doses and also non-uniformity in the dose distributions. It should be appreciated that these TCP values really represent a patient averaged value, for $\alpha = 0.35$ Gy^{-1} and thus not actually appropriate to the individual patient, whose α -value was unknown[9].

5.3 NTCP CALCULATIONS

The Lyman-Kutcher-Burman model was used for the calculation of the normal tissue complication probability. The critical organs considered were the spinal cord, the eye and the lens. All the normal tissue complication calculations for patients with 3-D plans resulted in a probability of 0 % except for two patients who had NTCP values of 0.4 %

and 1.4 % for the lens. The results of NTCP calculations are not tabulated since they all yielded a probability percentage of near 0 %.

For this study the NTCP parameter sets (m, n, TD_{50}) used were from the compilation of dose-response data by Emami et al. (1991). Unfortunately, the latter data is not statistical in nature thus uncertainities in the parameter values are indeterminate, as are the corresponding uncertainities in the calculated NTCPs[27].

NTCP calculations for patients treated using 2-D plans were not done, as the volumes of critical organs could not be determined from the information available in the treatment files.

5.4 UTCP CALCULATIONS

The uncomplicated tumor control probability (UTCP) was calculated using equation 3.7. Since the normal tissue complication probability was mostly 0 %, it followed that the uncomplicated tumor control probability (UTCP) was equal to the tumor control probability (TCP). Figure 5.6 shows BIOPLAN calculation results for the treatment plan of patient number 9 who was arbitrarily chosen. At the prescribed dose of 54 Gy, the TCP, NTCP and UTCP values are shown on the graph below.

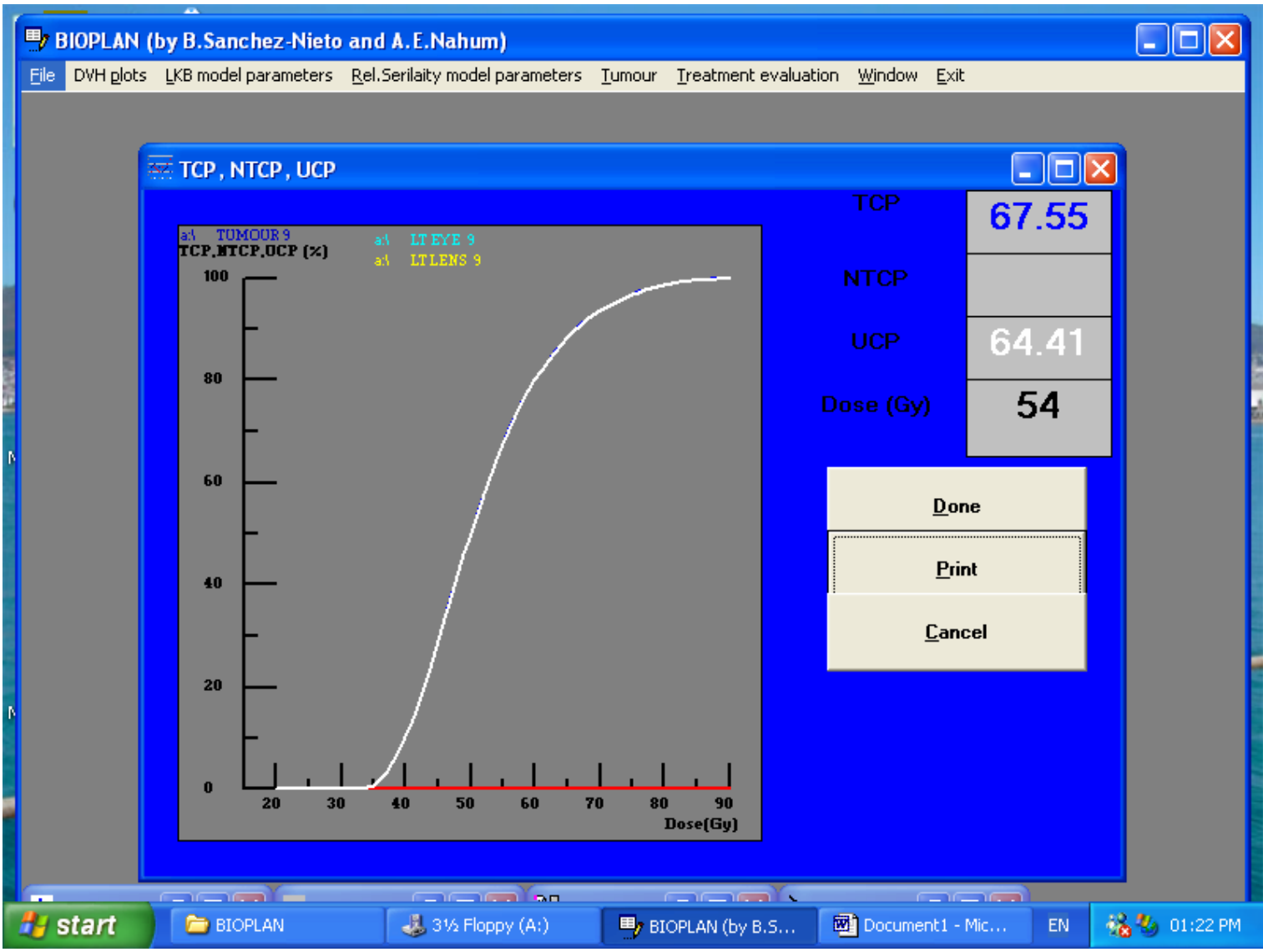


Figure 5.6: The graph shows the TCP, NTCP and UCP♠ for patient number 9.

For illustration purposes the same calculations were performed for patient number 3, who had an NTCP value of 1.4 % for the spinal cord. The results are shown in Figure 5.7.

♠ UCP is the same as UTCP

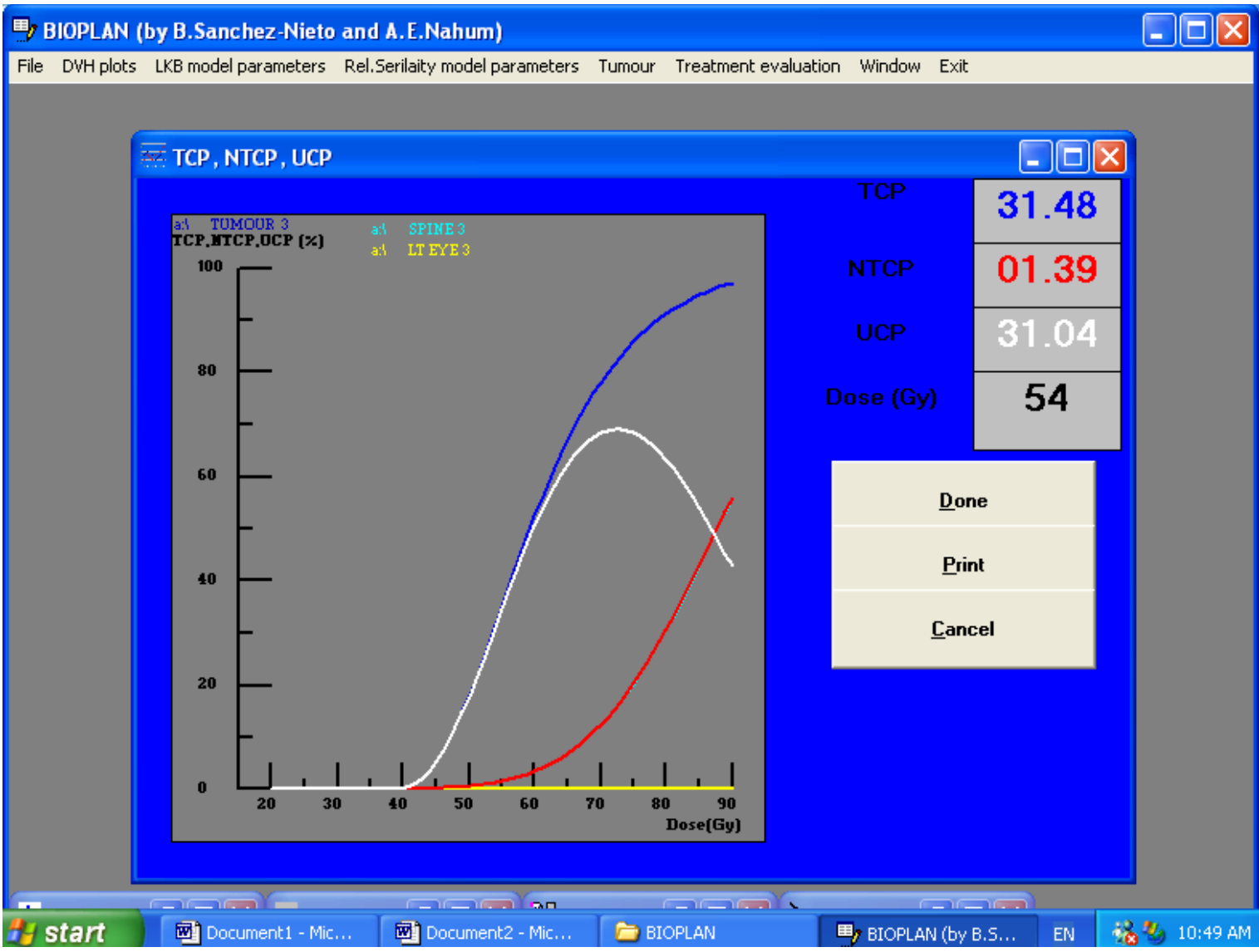


Figure 5.7: The graph shows the TCP, NTCP and UCP♠ for patient number 3.

This shows that given a tumor DVH, the dose, TCP, NTCP and UCP could be optimised.

♠ UCP is the same as UTCP

5.5 TCP VERSUS CELL RADIOSENSITIVITY

Theoretical models must be compared to clinical data whenever possible. The effect of α, the cell radiosensitivity on tumor control probability was tested on an arbitrarily selected patient. Each value of α was assigned three values of standard deviation in α (namely 0.00; 0.04 and 0.07). The graph for α = 0.35 has a slope which approximates the expected clinical response and also the slope for sigma – alpha (σ_α i.e. standard deviation in α) = 0.07 looks more realistic, which in essence validates the choice of these parameters (See 4.3.2). The curve with sigma-alpha = 0.00 is steep in all curves and besides it being an unrealistic representation of clinical outcome, it is not correct to assume that all tumors have the same radiosensitivity.

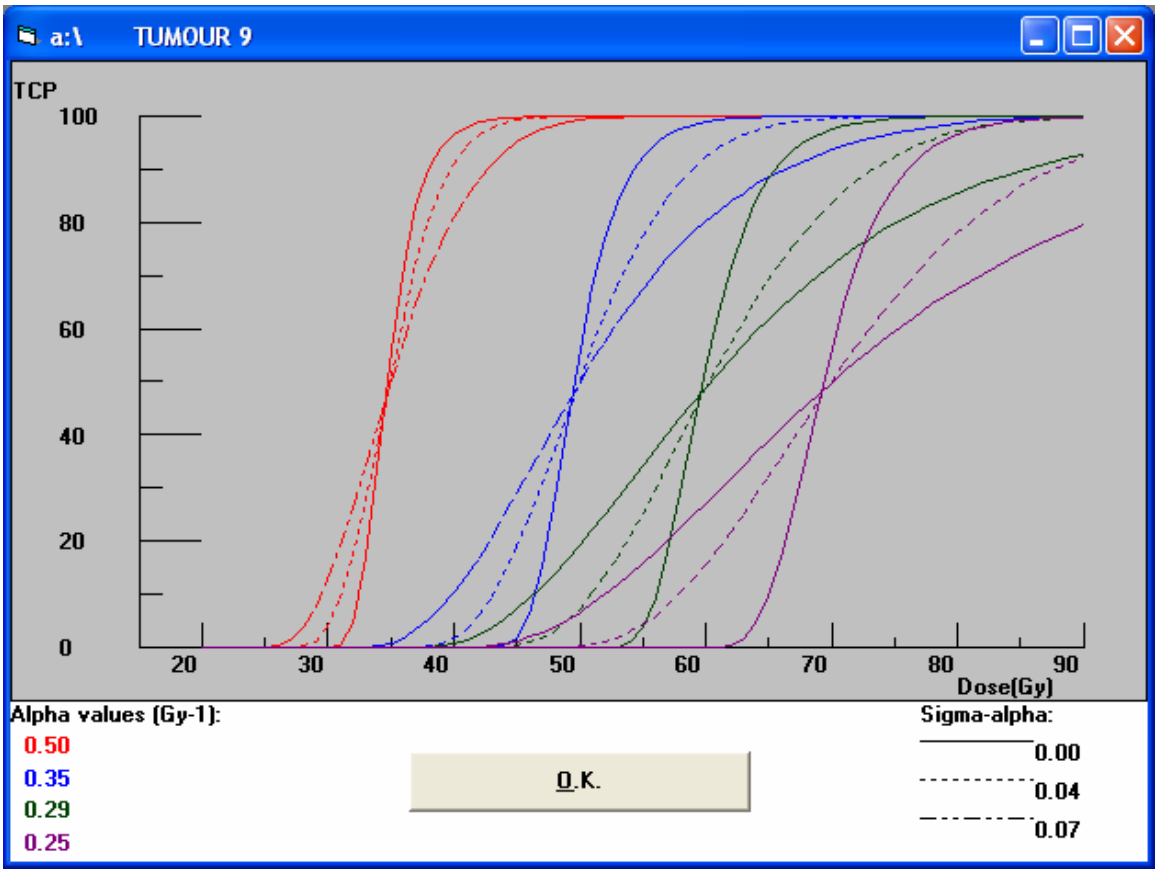


Figure 5.8: Shows how TCP varies with cell radiosensitivity.

5.6 DELTA-TCP FUNCTION

The effect of "hot" and "cold" spots was tested using delta-TCP function on the software. A "hot" spot is defined as an area inside the target area, which receives a dose considered significantly higher than the specified or prescribed target dose [28]. A "cold" spot is an area in the target area, which receives less than 95 % of the desired dose. Generally it was found that a hot spot would increase the TCP value and the reverse was generally true for a cold spot.

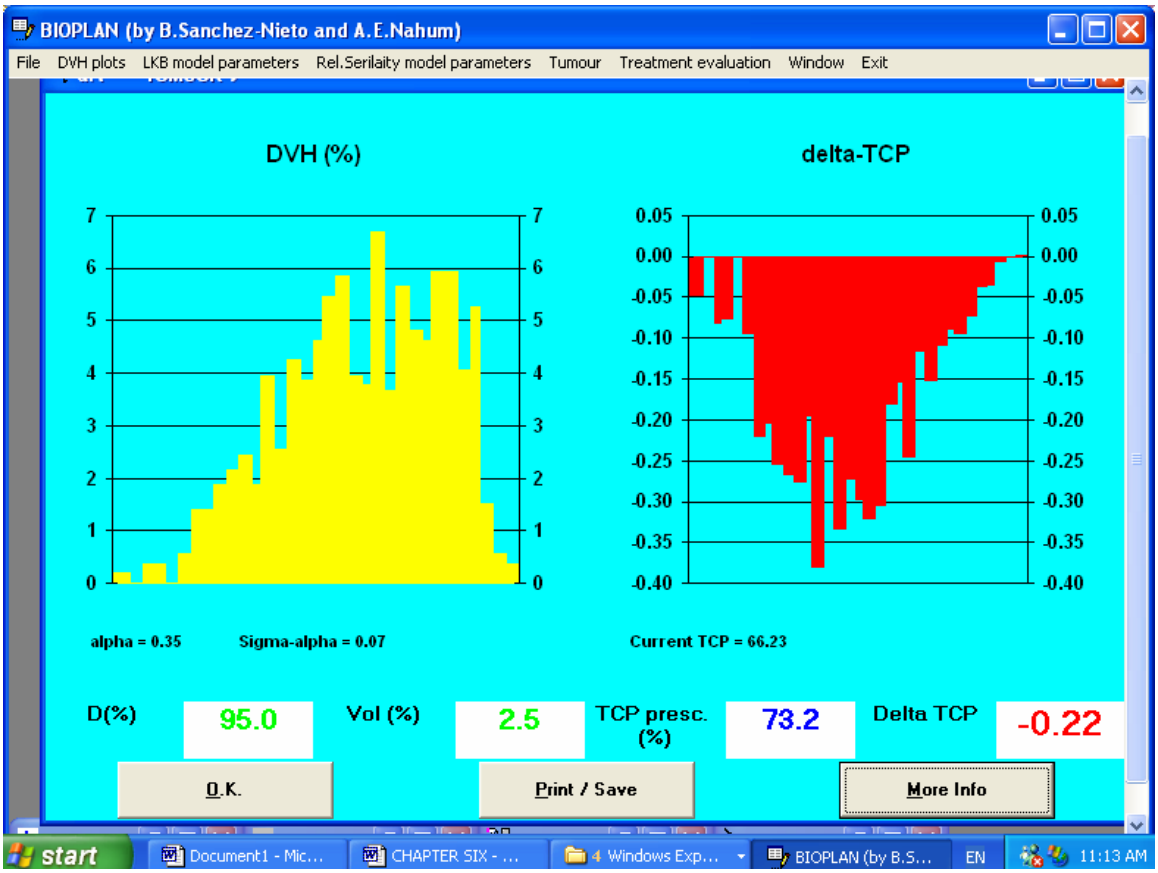


Figure 5.9: Shows a window from BIOPLAN using the delta TCP function

Thus, this function can be used to ascertain the magnitude by which the TCP increases when the size of a "hot" spot is increased or alternatively by how much it is possible to increase the size of a "cold" spot before the TCP decreases appreciably. Despite the fact

that the delta-TCP function gives valuable information, its major shortfall is its lack of additivity[29], thus, it is impossible to analyze the net effect on the TCP by changing the dose delivered to more than one fractional volume at the same time.

5.7 STATISTICAL ANALYSIS OF PROGNOSTIC FACTORS

The prognostic factors that have previously been associated with the 2 year- and 5 year overall survival of patients treated with radiation treatment were tested using the Cox Proportional Hazards regression method[30-31]. This was accomplished by using an online *Java Script* implementation of a statistical iterative method for Cox proportional hazard survival regression[32]. The effect of the other treatment modalities used in combined therapy could not be assessed, but it must be recognized that the patients also may have benefited from chemotherapy agents.

The following prognostic factors were analyzed, namely,

a) Age of the patient
b) Histology
c) Tumor volume
d) Primary site of the tumor
e) Timing of initiation of radiotherapy treatment
f) Total delivered dose
g) Sex of patient

In addition the effect of the treatment plan type (i.e. three-dimensional versus two-dimensional plans) was tested on the 5-year overall survival. A p-value of 0.05 and below was generally considered to be statistically significant. Table 5.4 shows the statistical results obtained.

Table 5.4: A statistical significance search for prognostic factors in rhabdomyosarcoma patients treated with external beam therapy.

Prognostic factor	2 year overall survival	2 year overall survival	5 year overall survival	5 year overall survival
	p- value	Hazard Ratio	p- value	Hazard Ratio
Age	0.1689		0.8584	
Age[⊗]	0.1041	6.1538	0.5657	1.3462
Histology	0.9519	0.0000	0.4152	1.5625
Tumor volume	0.3306		0.2560	
Site of tumor	0.7156	0.6400	0.7021	1.2800
Timing of initiation of radiotherapy	0.6949		0.3067	
Prescribed dose	0.5301		0.9631	
Sex	0.4597	2.2857	0.4389	1.5714
Plan type (3D versus 2D plans)	0.9615	0.0000	0.5994	0.7500

The conclusion from the above table is that none of the tested prognostic factors were found to be statistically significant. The effect of these potential prognostic factors can be explained by the hazard ratio. The hazard ratio compares two groups differing in treatments or prognostic variables. The computation of the hazard ratio assumes that the ratio is consistent over time and that any differences are due to random sampling.

The hazard ratio for age was calculated to be 1.3462 at 5 years post treatment, which means that the hazard (i.e. poorer survival) associated with children above 6 years of age was 1.3462 times greater than those below the age of 6.

[⊗] patients sorted into two groups those aged 6 years and below and those above 6 years of age

The hazard ratio for histology was calculated to be 1.5625 at 5 years post-treatment, which means the hazard associated with children having alveolar rhabdomyosarcoma was 1.5625 times greater than those having embryonal rhabdomyosarcoma.

Hazard ratio calculations showed that patients who had parameningeal rhabdomyosarcoma had a poorer survival (5 years after treatment) than those with orbital rhabdomyosarcoma.

In addition, the hazard ratio relating to sex indicates that female patients had a better survival rate than male patients. This study established that for this patient population, those patients with two-dimensional plans had a better survival rate than those with three-dimensional plans.