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Pre Operative Chemotherapy In Wilms Tumour- Its Effectiveness - A Prospective Institutional Study

KEYWORDS: Green Housing, Green House Rating, Jerry Buildings, IGBC, AGBR

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ABSTRACT ***Purpose :*** *NWTS(National Wilms Tumour Study)currently describes following indications for pre operative chemotherapy. • Extensive Vena Caval Involvement • Bilateral Tumours • Single Kidney • Stage Iv Disease However tumour size and incidence of tumour spillage has not been addressed for pre operative CT.* ***Methods :*** *We have done a prospective study at our institute to see the advantages of complete tumour excision without rupture , decrease in size of tumour with 6 weeks of pre op CT in 20 patients. Details of initial evaluation ,pre op CT, pathological findings and surgical resection constitute this report.* ***Results :*** *• All our patients who received pre op CT underwent complete surgical resection. • Incidence of tumour rupture was less than 10 %. • Significant shrinkage of tumour size was noted in more than 90 percent of cases. • Post operative histology showed negative tumour margins in most of the cases. • Downstaging of histology noted. • There was no requirement of post operative radiotherapy in majority of cases in our study.* ***Conclusions:*** *Pre op CT allowed for complete tumour resection with negative margins, reduced incidence of tumour rupture and reduced need for post operative radiotherapy.*

INTRODUCTION :

Wilms' tumor is one of the commonest tumors of childhood that cause significant morbidity and mortality. Dramatic improvement in survival have occurred as a result of advances in anesthesia, surgical techniques, irradiation and chemotherapy. Treatments are now based on several multicentric trials conducted by International Society of Pediatric Oncology (SIOP) in Europe and NWTSG in US. The SIOP trials largely focus on the issue of preoperative chemotherapy.

In neoadjuvant chemotherapy complete surgical removal of shrunken tumour is facilitated, tumour rupture caused by surgical procedures is minimized or avoided, and micro metastases not visible at diagnosis are treated as early as possible(2). This is more appropriate in children with bilateral Wilms' tumour and patients with single kidney in whom parenchymal sparing procedures are desirable (4). Patients with inoperable tumors and extensive intravascular tumor extension can also benefit from this approach. In addition, the response to treatment can be measured individually by tumour volume reduction or the percentage of therapy- induced necrosis at the time of surgery in histologic specimen. These findings serve as early individual prognostic parameters and can be further stratified and individualized.

The SIOP advocates preoperative chemotherapy of vincristine and actinomycinD for a period of 4 weeks in local tumours (Stage I and II), and 6 weeks in advanced tumours with addition of adriamycin at 1st and 5th week. The surgery is undertaken at 5th week in local tumors and 7th week in advanced tumors.(3)

Based on surgical staging, histologic features and tumour shrinkage, these tumours are classified into low, intermediate and high risk groups.

The staging criteria (Conventional NWTS staging)(1)(5)

Stage-I

- Tumour limited to kidney and completely excised.
- Renal capsule has intact outer surface.
- Tumour was not ruptured or biopsied prior to removal.
- Vessels of renal sinus are not involved.
- No evidence of tumour at or beyond margins of resection.

Stage-II

- Tumour extended beyond kidney but completely excised.
- There may be regional extension of tumour (penetration of renal sinus or renal capsule)
- The blood vessels may contain tumour.
- Tumour biopsied or tumour spill during surgery confined to flank and does not involved peritoneal surface.
- No evidence of tumour at or beyond margins of resection.

Stage-III

- Residual non hematogenous tumour confined to abdomen.
- Lymph nodes within the abdomen or pelvis are involved.
- Tumour penetrated through peritoneal surface.
- Tumour implants found on peritoneal surface.
- Tumour cells found at margin of surgical resection on microscopic examination.
- Tumour not completely resectable because of local infiltration into vital structures.
- Tumour spill into the pertonial cavity during the surgery.

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Stage-IV
- Distant metastases in lung, liver, bone, brain etc.,
- Lymph nodes outside the abdominopelvic region.

Stage-V
- Bilateral renal involvement
- Each side staged according to the above criteria.

Based on the above staging criteria tumour is classified as following (classification after preoperative chemotherapy-SIOP criteria)

- Low risk
- Intermediate risk
- High risk

Low risk
- Stage-I and Stage-II
- Tumour completely necrotic (100%)
- Mesoblastic nephroma.

Intermediate risk
- Histology of epithelial, stromal or mixed types.
- Necrosis between 66-99%.
- Focal anaplasia.
- Tumour volume < 400 ml after CT.
- High risk
- Blastemal type
- Necrosis < 66%.
- Diffuse anaplasia.
- Tumour volume > 400 ml after CT.

Treatment protocols are

	STAGE-I	STAGE-II	STAGE-III
LOW RISK	NO FURTHER TREATMENT	AV-2	AV-2
INTERMEDIATE RISK	AV-1	DOX + R< DOX -	RT/DOX + R< RT/DOX -
HIGH RISK	AVD	HIGH RISK + RT	HIGH RISK +RT

AV -1 -- ACTINOMYCIN D +VINCRISTINE for 18 weeks

AV -2 -- ACTINOMYCIN D +VINCRISTINE for 24 weeks

DOX+ -- DOXORUBICIN for unfavorable histology

DOX- -- No DOXORUBICIN

RT -- RADIOTHERAPY

In this study, the role of preoperative chemotherapy and their surgical outcome has been studied in those children that presented with locally advanced tumors STAGE 1 where the tumour size is large (>15 cms and abutting greater vessels but not infiltrating) during the years 2001-2014

MATERIALS AND METHODS :

Materials

During the period from 2001-2014, 20 children (15 Female and 5 male) with Wilms' tumour were treated with pre-operative chemotherapy. These included the children in whom the size of the tumor was very large (MORE THAN 10 CMS IN SIZE)and engulfing or adherent to greater vessels.

Methods

All these children underwent routine CBP, USG abdomen to assess the size of tumor, intravascular extension and for any secondaries, Chest XRay to rule out lung metastasis and CT scan to assess the tumor in relation to the adjacent structures and intravascular invasion. Preoperative FNAC was done to know the pathological diagnosis.

All these children were given preoperative chemotherapy for 6 weeks which include 1 dose of Actinomycin D (45 mg/kg) at 0 week. Adriamycin (1.5 mg/kg) at 1st and 5rd week and Vincristine 0.05 mg/kg for 6 weeks.

After a 6 week period of chemotherapy all these children were reassessed with USG abdomen and CT scan abdomen to know the extent of tumor.

Surgery was done at 7th week. Chemotherapy was continued from 9th week again for a total period of 18 weeks in stage-I and stage-II favourable histology types and for 24 weeks (upto 27 weeks) for unfavourable histology group of any stage .

Based on histopathological features following surgery, radiotherapy was given in five children.

All these children after completion of 24 weeks chemotherapy were followed with routine CBP, Ultrasound abdomen every three months in 1st year and every 6 months in 2nd year.

These children were assessed for following variables
- Reduction in size of tumor
- Tumor rupture during surgery
- Tumor recurrence or distant metastasis during follow up

+	Age	Sex	Preoperative USG/CT size & features	FNAC PICTURE	Intra operative size & features	Tumor rupture	HPF report	Result
1	5 Yrs	F	10 x 12 cm x10 cm (Rt) renal mass adherent to major vessels. No involvement of IVC, Renal vein	Predominantly blastemal elements Foci of epithelial and mesenchyma elementsl	3 x 3 cm	No	10% viable tumor Tripharic Wilm's	No RT given onfollow up. no recurrence
2	12 Yrs	M	16 x 10 x 10 cm tumor compressing (Rt) kidney replacing entire kidney	Highly cellular blastemal and mesenchymal elements Biphasic Wilms	3 x 1 cm SOL in upper pole (Rt) kidney	No	10 % Viable tumor Biphasic - FM	No RT no recurrence
3	3 Yrs	F	10 x 8x8 cm(Rt) middle and upper poles PCS dialated and involved with tumor	Biphasic variant blastema and mesenchymal elements seen	5 x 2 cm (Rt) middle/lower poles	No	10 % Viable tumor FM – Biphasic	No RT no recurrence

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4	3 Yrs	F	10 x 9 x7cm SOL in upper middle lobes (Lt) compressing proximal ureter	Triphasic Wilms	4 x 3 cm upper & Middle lower (Lt) kidney	No	20 % viable tissue Triphasic - FM	No recurrence no RT given
5	8/12	F	Wilms (Lt) 9 x 5 x 4.5 cm upper and middle poles.	Biphasic Wilms	4 x 2 cm (Rt) completely	No	10% viable tumour. biphasic FH	No Recurrance noRT given
6	1 Year	M	10 x 10 x8cm upper middle lobes (Lt) IVC involved.	FNAC Triphasic Wilms	3 x 1 cm in (Lt) upper/middle segment. No IVC involved	No	Triphasic –UH 30 % viable tissue	Subjected to RT no recurrence
7	1 ½ Year	M	12 x 10 x10 cm (Rt) –entire kidney replaced	Triphasic FH	6 x 4 cm no tumor rupture	No	Triphasic FM FH	No radiotherapy given Developed Lung mets on follow up
8	5 yrs	F	left Willms with haematuria 14 x 10 x 7 cm. involving Renal hilum and pelvis and left upper pole	FNAC triphasic variant FH	Shrinkage of tumour with tumour adherent to diaphragm.3x3 cms size	No tumor spill	triphasic variant FH	No radiotherapy given.on follow up. no recurrence
9	3yrs	F	15 x 12 x 8 cm (Rt) with gross anaemia,entire kidney replaced	FNAC undifferentiated	10x8 cms surroundingtissue tumor infiltration	Tumour spill present	Less than 30 %of tumour tissue with diffuse anaplasia. necrotic cells predominant	radiotherapy given. pt. on regular follow up.
10	4 yrs	M	11x8x6 cms from upper pole of left. kidney	FNAC-Triphasic variant	7x5 cms size tumour.adherent to perirenal tissues.	No	Triphasic ,focal capsular involvement seen	radiotherapy given
11.	3 yrs	F	10x8x6 cms tumour in lower pole of lt kidney	FNAC-Biphasic variant	6x5x4 cms complete tumour excised	No	Biphasic cystic degeneration with extensive necrosis. focal anaplasia present	No radiotherapy given.no recurrence
12	6 mon	F	15 x15x13 cms large tumour replacing entire rt.kidney renal vessels not involved	FNAC-Triphasic variant	9cms x9cms x8 cms.tumour excised completely	No	Triphasic with extensive necrosis. No capsular infiltration.	No radiotyherapy given. on follow up
13	5 mon	F	10 x7x 5 cms arising from lower pole of left kidney.ivc and renal vessels not involved.	FNAC –TRIPHASIC PATTERN	7 x6 x6 cms.tumor excised completely	No	Triphasic variant with areas of anaplasia	No radiotherapy given.on follow up
14	9 mon	F	11 x8 x8 cms occupying whole right kidney.no renal vesseland ivc involved.	Blastemal predominant	9 x8 x5 cms .tumour excised completely	No	Predominantly blastemal elements and anaplasia	Radiotherapy given.on follow up
15	2 ½ yrs	M	10 cms x 9cm x7 cm tumour arising from upper pole	Biphasic variant	8 x 5 x 5 cms size tumour completely excised.	No spill	Biphasic tumour faourable histology	No radiotherapy On follow up
16	3 yrs	F	11 x8 x6 cms from lower pole of right kidney	Triphasic variant	8 x6 x5 cms size tumour.completely excised	No tumour spill	Triphasic tumour. favourable histology.no capsular invasion	No radiotherapy On follow up
17	1 yr	F	12 x10 x8 cms-from upper pole of rt.kidney.no vascular invasion	Triphasic variant	5 cm x5 cm tumour from upper pole of right kidney. partial upper pole nephrectomy done	No spill	Triphasic favourable histology.no capsular invasion.normal renal parenchyma is seen outside the capsule	No radiotherapy given.on follow up.
18	1 yr	F	9.5 x7 x 6 cms arising from right kidney. no vascular involvement	Triphasic variant	7 x6 x 5 cms tumour arising from upper and medial pole of right kidney. tumour completely excised.	No spill	Triphasic differentiated type.no capsular invasion	No radiotherapy given.on follow up

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19	2 yrs	F	17 x 7 x4 cms tumour arising from middle and lower pole of right kidney	Triphasic variant	10 x8 x 4 cms tumor .completely excised.	No spill	Triphasic variant. favourablehistology.no capsular invasion	No radiotherapy given.on follow up
20	2 yrs	M	12 X9 X6 CMS arising from lower pole of right kidney	Triphasic pattern	9 x6 x6 cms tumor completely excised	No tumour spill	Triphasic variant. capsular invasion into adjacent renal tissue.vascular emboli seen. Large areas of necrosis.	Radiotherapy given..on follow up

Table 2.

Patients studied -20
Excluded from trial (in study) - Stage IV & V - Tumor too small (clinician's estimation) -Doubt in diagnosis -Registered after nephrectomy

Table 3 : Characteristics of Patients

No. of patients - 20
Age at nephrectomy (mean) - 3 years
Sex Male - 6 Female - 14
Side affected Right - 13 Left - 7
Mean size of the tumor* Length (cm) - 11 cms Width (cm) - 9cms
Site of tumor Poles of kidney Upper pole - 8 Lower pole - 5 Midzone - 3 (includes one case in hilum+2 cases upper pole+I case lower pole) Massive - 6

Table 4

Effect of Preoperative Treatments on the Primary Tumor

Major reduction of the tumor size after preoperative treatment (clinical)	In all of the cases significant reduction in size
Tumor rupture during surgery (No. of cases) 1	(necrotic material spilled during sharp dissection of densely adherent tumour to retroperitoneum)

Table 5.

Site of Recurrences after treatment	In one case on follow up developed localrecurrence and lung metastasis

RESULTS:

All our patients who received pre op CT underwent complete surgical resection .

Incidence of tumour rupture was less than 10 %.

significants hrinkage of tumour size was noted inmore than 90 percent of the cases.

Post operativehistology showed negative tumour margins in most of the cases.

Downstaging of histology noted .

There was no requirement of post operative radiotherapy in majority of cases in our study.

CONCLUSIONS:

Wilms tumour in children responds well to chemotherapy medication.hence preop ct has a key role in management of these cases.(6) we have utilized this to study its effect on large tumours which were thought to be inoperable pre operatively.in our instituitional study it was found that Pre op CT allowed for complete tumour resection with negative margins, reduced incidence of tumour rupture during study and reduced the need for post operative radiotherapy.

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