KAPOSI SARCOMA

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INTRODUCTION

Moritz Kaposi (1837 – 1902)

Idiopathic multiple pigmented sarcoma of the skin – 1872

Extremely rare pre-HIV/AIDS era

Commonest malignancy affecting HIV-infected individuals (immunocompromised)

Gaps in understanding KS still huge

SUB-TYPES

Forms of KS	Clinical presentation	Risk factors	Progression
AIDS-related (also known as epidemic)	Cutaneous lesions (100%) Mucosal lesions (20%) Visceral involvement (15%) Tumour-associated oedema	Declining CD4 cell counts (Improves with the use of cART)	Indolent or aggressive course (Regresses with cART)
Iatrogenic	Cutaneous lesions Mucosal and visceral disease rare	Solid-organ allograft (Risk higher in multi-organ transplants and greater HLA mismatching)	Usually localized (Regresses with reduction / modification in immunosuppression)
Endemic	Children – lymph nodes with lymphedema, visceral involvement Adults –lower-limb lesions that resemble classic KS	Sub-Saharan Africa Seronegative for HIV	Children – aggressive with Adults – indolent or locally invasive
Classic (also known as sporadic KS)	Confined to lower limbs with few lesions Visceral and mucosal disease rare	Middle-aged and elderly individuals Men > women Middle East, eastern Europe and the Mediterranean	Usually indolent; rarely aggressive and disseminated
MSM without HIV infection	Any skin sites, usually with few lesions. Visceral and mucosal disease rare	MSM without HIV infection Young or middle aged Not immunocompromised	Usually indolent

Cesarman et al, Nat Rev Dis Primers 2019

STAGING

AIDS Clinical Trial Group (ACTG) Classification using TIS System

Pooled analysis from 34 trials (N = 281)

Criticism

- Old trials (1989 – 1995); did not use currently recommended cytotoxic drugs
- I-stage less relevant with HAART
- Data derived from 98% male patients

No AJCC system for KS

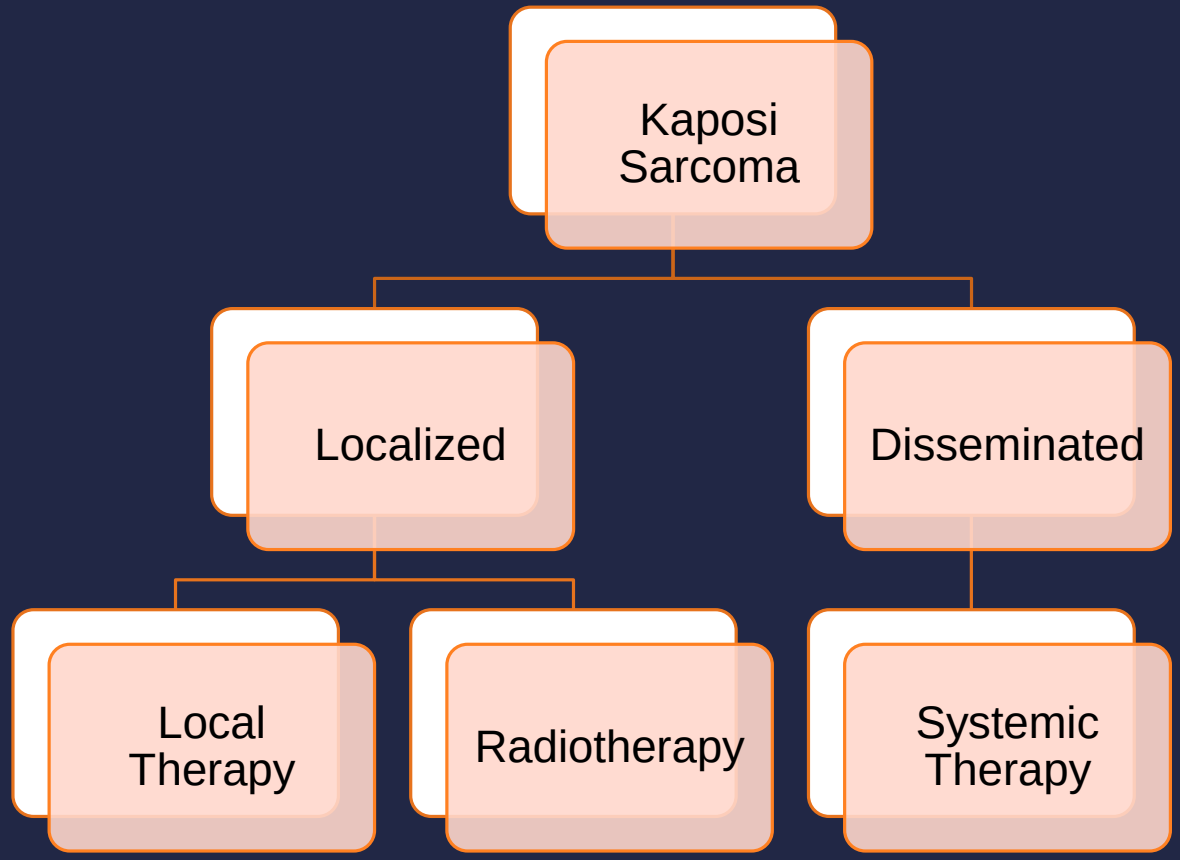
	Good risk ($_0$) (all of the following)	Poor risk ($_1$) (any of the following)
Tumour (T)	• Confined to skin and/or • Lymph nodes and/or • Minimal oral disease[a]	• Tumor-associated oedema or ulceration • Extensive oral KS • Gastrointestinal KS • KS in other non-nodal viscera
Immune system (I)	• CD4 ≥200/μL	• CD4 <200/μL
Systemic illness (S)	• No history of OI or thrush • No "B" symptoms[b] • Performance status ≥70 (Karnofsky)	• "B" symptoms present • Performance status <70 • Other HIV-related illness (e.g. neurologic disease, lymphoma)

[a] Minimal oral disease is non-nodular KS confined to the palate

[b] "B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhoea persisting >12 wk

Krown et al, J Clin Oncol 1997; Groopman, Uptodate 2021

MANAGEMENT



Options of Systemic Therapy

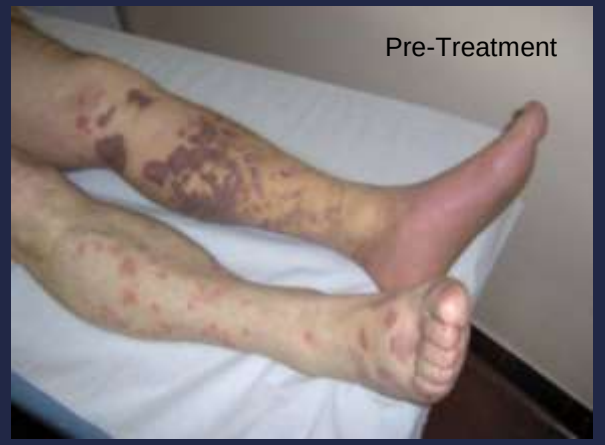
1. Highly Active Anti-Retroviral Therapy (HAART) / Combined Anti-Retroviral Therapy (cART)
2. Cytotoxic Chemotherapy
3. Immunotherapy
4. Targeted Therapy

GENERAL APPROACH

Lack of concept of cure in KS
- No available treatment to eradicate latent KSHV

Treatment goal is palliation (use the term with caution!)
- Relieving symptoms that interfere with ADL
- Improve function
- Delay / prevent disease progression

Quality of data is poor
- Very few prospectively designed phase II clinical trials
- Trials with poor accrual
- Retrospective case series and case reports



Zustovich et al, Anticancer Res 2013

OBSERVATION

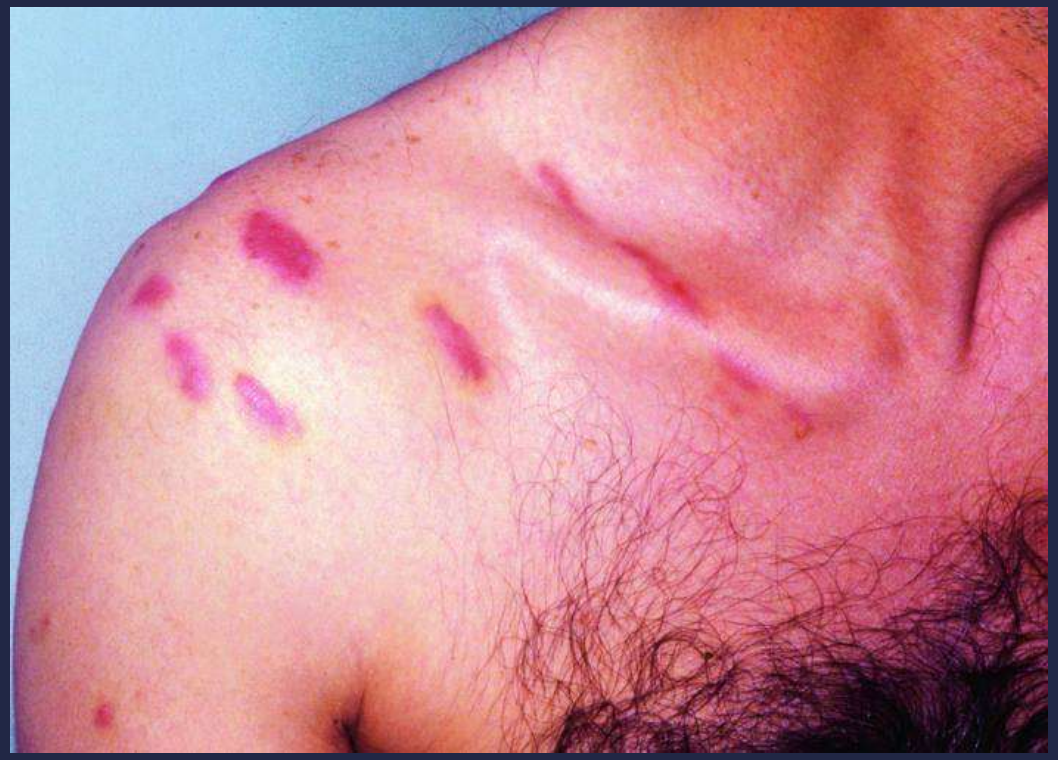
Acceptable approach

- Limited number of lesions
- Multiple localized lesions
- Lesions do not impair function
- Typically classical KS (but also possible in other sub-types)

Assessment of compliance to follow up

Frequent follow up schedule (ideal / recommended schedule not available)

Method of surveillance – clinical vs imaging



Brenner et al, Intl J Oncol 1999; MSD Manual Prof Ed 2022

LOCAL THERAPY

Single symptomatic lesion
- Surgical excision
- Curettage and topical hydrogen peroxide

Multiple localized lesions
- Cryotherapy
- Laser therapy
- Cosmetically favourable

Nodular classical KS <10 lesions
- Intralesional chemotherapy: vinblastine, bleomycin, vincristine, doxorubicin
- Intralesional interferon-α-2a

Topical Therapy
- Cis-retinoic acid
- Imiquimod
- Rapamycin
- Timolol
- Silver nitrate
- Nicotine patch

Regnier-Rosencher et al, J Am Acad Dermatol 2013

LOCAL THERAPY

Radiotherapy

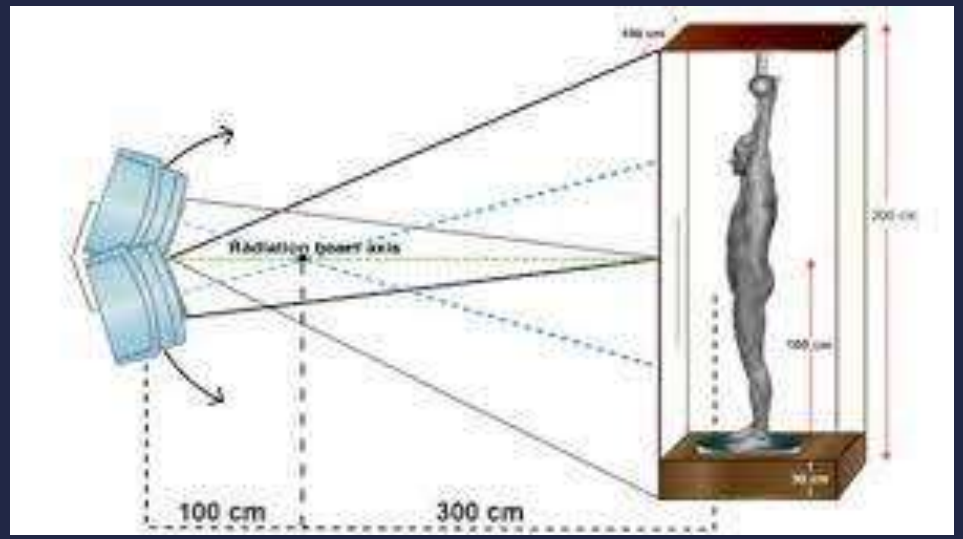
- KS is highly radio-sensitive
- Different energy: cobalt-60, kV photons, MV photons, electrons
- Dose range 6Gy – 60Gy (6Gy single and 30Gy/10# commonest)

Suitable for

- Solitary lesions
- Lesions confined to one area
- Oligo-progressive disease

More extensive lesions may be treated with

- Total / Near total skin electron therapy
- Waterbath radiotherapy technique (hands/feet)
- Helical tomotherapy with virtual bolus



Groopman, 2022. UptoDate

SYSTEMIC THERAPY AIDS-RELATED KS

50% of KS spontaneously respond to immune reconstitution

HIV suppression with HAART

- Treatment-naïve
- Progression of HIV while on 1st line HAART
- HAART reduces new incidence of KS
- HAART reduces severity of KS

Protease inhibitors

- Anti-angiogenic properties
- Encouraging pre-clinical data
- Outcomes not improved in KS compared to non-protease inhibitor containing HAART

Schneider & Dittmer, Am J Clin Dermatol 2018

SYSTEMIC THERAPY
CHEMOTHERAPY

Indications

- Widespread cutaneous lesions
- Progression on local therapy or HAART
- Extensive oedema
- Symptomatic visceral involvement
- Symptomatic mucosal lesions
- KS-IRIS

Single agent chemotherapy

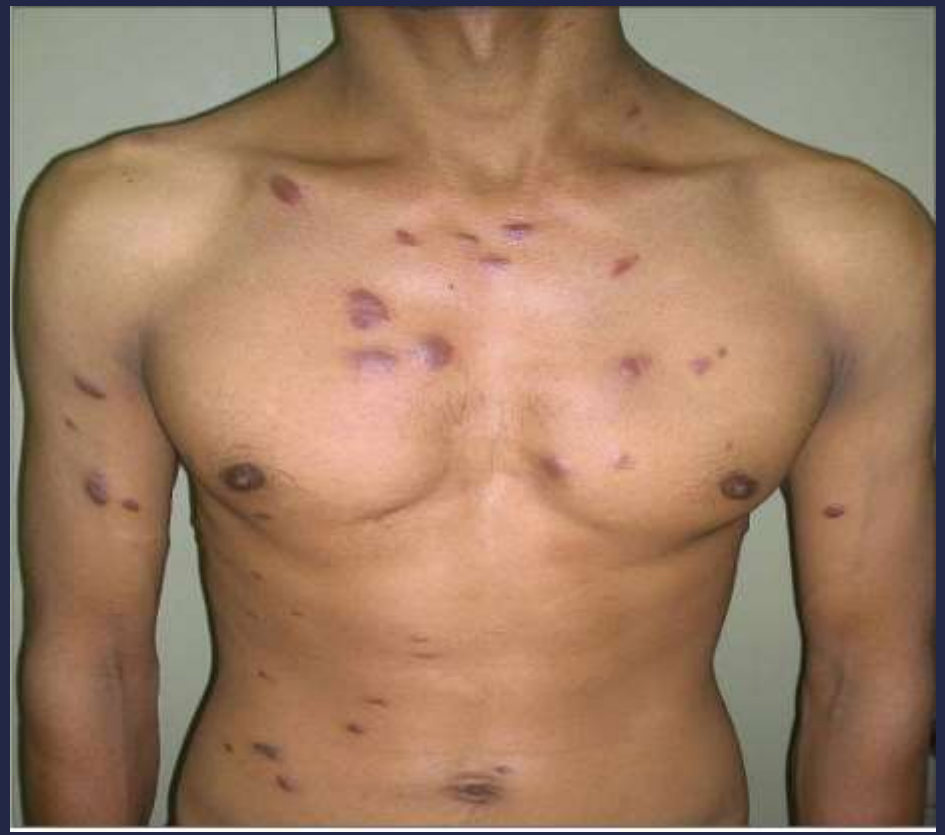
- RR 40 – 70%
- Etoposide, Teniposide, Vincristine, Bleomycin

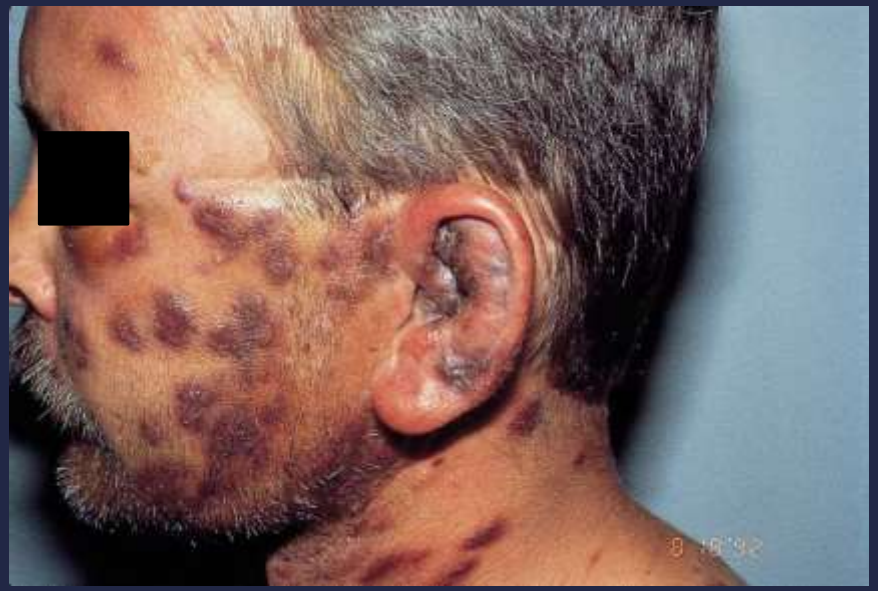
Combination chemotherapy

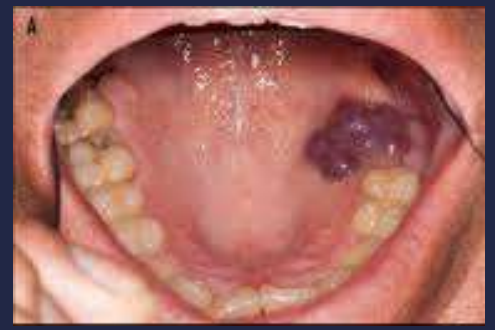
- RR 60 – 90%
- Commonest: Doxorubicin + Bleomycin + Vincristine (ABV)

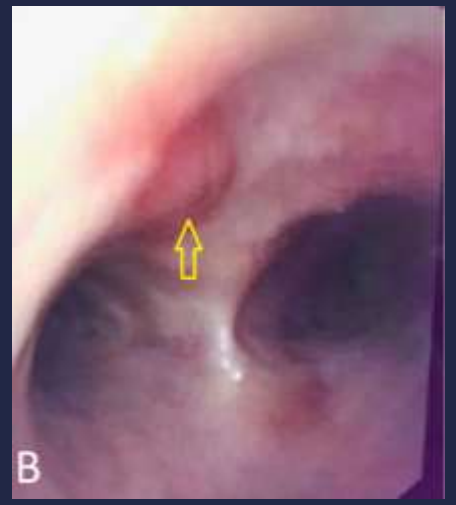
Groopman, 2022. UptoDate, Lee & Mitsuyasu, Haem/Oncol Clinics North America 1996

CLINICAL MANIFESTATION









Shah & Abu Salleh, Medical Images 2019; Bhatia et al, Indian J Derm Ven Lep 2017; MSD Manual Medical Images; Scheetz et al, Cureus 2020

SYSTEMIC THERAPY AIDS-RELATED KS

Pre-HAART Era

- Use of chemotherapy either as single agent or combination showed some clinical activity

HAART alone vs Chemo+HAART

- Trend towards improved survival outcome with combination of Chemo+HAART

Chemo+HAART vs Chemo+HAART

- No significant difference regardless of the type of chemotherapy used

Commonly studied regime:

- ABV (Doxorubicin, Bleomycin, Vincristine)
- Liposomal daunarubicin
- Pegylated liposomal doxorubicin

Gbabe et al, Cochrane Databse Systematic Reviews 2014

LIPOSOMAL ANTHRACYCLINES

Study	N	Arms	RR (%)	Severe Toxicity (%)
Northfelt et al	133	ABV	25	94
		PLD	46	92
Stewart et al	241	BV	23	15
		PLD	59	16
Gill et al	232	ABV	28	32
		Liposomal daunarubicin	25	17
Cianfrocca et al	73	Paclitaxel	56	84
		Liposomal doxorubicin	46	66
Cooley et al	79	Liposomal daunarubicin	32	63
		PLD	55	68

Groopman, 2022. UptoDate

ABV: Doxorubicin, Bleomycin, Vincristine; BV: Bleomycin, Vincristine; PLD: Pegylated Liposomal Doxorubicin

PACLITAXEL

Open label, non-inferiority study in AIDS-related KS

- Paclitaxel vs Oral etoposide vs BV
- Etoposide inferior to Paclitaxel and BV
- BV caused more neuropathy than Paclitaxel

Use in Classical KS is extrapolated

Highly effective in rapidly progressing disease

More toxic than PLD

- Pacli: Hair loss, neuropathy, neutropaenia
- Readily available in resource-limited setting
- Versatile administration schedule

3weekly schedule may be better than 2weekly schedule

Caution with Paclitaxel

- Pre-medication with glucocorticoids
- Metabolism through CYP450

Krown et al, Lancet 2020; Krown et al, Uptodate 2022

IMMUNOMODULATION

Mechanisms of action of IFN-alpha

- Anti-angiogenic
- Anti-viral
  - Suppress mRNA translation into protein
  - Prevents assembly of intact virus
  - Synergistic
- Immunomodulatory
  - Promotes differentiation of immune cells

More effective if CD4 counts >150/mcL

Slow response (4 – 6 months)

Response rate = 40%

Not recommended

- IFN-alpha + chemotherapy combination
- High dose IFN-alpha (>20 MU/week)

IFN-beta have also been used

Toxicity

- Neutropaenia (high dose)
- Fatigue
- Flu-like syndrome
- Depression

IMMUNOMODULATION

Retinoic Acid

- Down-regulates IL-6; prevents proliferation of KS
- Induces apoptosis at high doses (not clinically achievable)
- Inhibits replication of KSHV

At least 8 case reports published with good outcome

- Oral isotretinoin (1mg/kg BID)
- Oral alitretinoin (100mg/m2 OD)
- Oral acitretin (35mg OD)

Side effects

- Skin (rash, erythema, dryness)
- Rarely hepatic dysfunction

IMMUNOTHERAPY

Study	Agent	N	Response Rate (%)
Galanina et al 2018	Nivolumab	8	63
Zer et al 2020	Ipilumumab + Nivolumab	15	66
Deylon et al 2022	Pembrolizumab	30	71

*Excluded HIV-related KS

ANTI-ANGIOGENIC AGENTS

Study	Agent	N	Response Rate (%)
Koon et al 2005	Imatinib mesylate	5	80
Escalon et al 2006	Thalidomide	20	40
Uldrick et al 2012	Bevacizumab	17	31
Polizzotto et al 2016	Pomalidomide	22	60

SYSTEMIC THERAPY IATROGENIC KS

Immune reconstitution by reducing immuno-suppressant

- Improves KS
- Increases risk of graft vs host disease

Switch from cyclosporine to mTOR inhibitor

- Cyclosporin only targets T-cells
- mTORi targets T-cells, B-cells, endothelial cells and KS directly
- mTORi maintains immunosuppression while treating KS
- Commonly used: everolimus

- Note: mTORi has good clinical activity in KS regardless of immune status

Schneider & Dittmer, Am J Clin Dermatol 2018

QOL & PALLIATION

Theoretically improvement in QoL and symptoms palliation is established

Not well studied in most clinical trials

- No standard approach
- Inconsistency between general and KS-specific QoL
- Unavailability of pre-treatment scores

Cesarman et al, Nat Rev Dis Primers 2019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HKL
KECEMASAN
Parkir Awam
Keluar
Jalan Pahang
Kompleks Pakar
& Rawatan Harian
(SCACC)

Thank you